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No. 84-____

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

—v.—

CAROL LYNN WOODERSON,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF KANSAS

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38 pp

QUESTIONS PRESENTED

1. Does the Supremacy Clause preempt individual states from forcing makers of prescription drugs sold in interstate commerce to include warnings in the prescribing instructions found impermissible under federal law and at variance with the purposes of that federal law?

2. Does a refusal of a state court to make available to an out-of-state defendant that state's statute apportioning negligence among *all* parties to an occurrence constitute a denial of equal protection?

LIST OF PARTIES TO THE APPEAL IN THE SUPREME COURT OF THE STATE OF KANSAS

The names of all of the parties to the appeal in the Supreme Court of the State of Kansas are provided in the caption to this petition. Sup. Ct. R. 21.1(b). Ortho Pharmaceutical Corporation is a wholly owned subsidiary of Johnson & Johnson. Pursuant to Rule 28.1, the following are all of the affiliates of Johnson & Johnson, other than wholly owned subsidiaries:

ens Biologicals, Inc.
Enzo Biochem, Inc.
Immunomedics, Inc.

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PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF KANSAS

OPINIONS BELOW

The opinion of the Supreme Court of Kansas dated April 27, 1984, reported at 235 Kan. 387, 681 P.2d 1038 (the "Opinion"), and its denial without opinion of the motion for rehearing by Ortho Pharmaceutical Corporation ("Ortho") on June 25, 1984, are reproduced in Appendix A. This was a direct appeal from the judgment entered by the trial court on a verdict returned in February 1983. On March 18, 1983 the trial court orally denied Ortho's motions for a directed verdict or in the alternative for a new trial (R. XL).[1]

1 Citations to " R. ____" are to the trial record; "pp. ____" refers to the trial transcript.

JURISDICTION

The opinion affirmed a judgment of $4,750,000 in an action for damages for personal injuries by Carol Wooderson, who claimed that oral contraceptives sold by Ortho and taken by her between 1972 and 1976 caused her acute kidney failure in June 1976 (R.III, p. 382). She asserted that Ortho failed to warn her prescribing physician of a suspected risk of acute kidney failure due to hemolytic uremic syndrome ("HUS"), and that this failure to warn caused her kidney failure. Verdicts of $2,000,000 in compensatory damages and $2,750,000 in punitive damages were returned (R.III, pp. 381-2). This court has jurisdiction to review the judgment under 28 U.S.C. § 1257(3).

CONSTITUTIONAL PROVISIONS INVOLVED

Article VI, clause 2 (Supremacy Clause):

> "This Constitution and the Laws of the United States which shall be made in pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the Supreme Law of the Land; and the Judges of every state shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding."

Amendment XIV:

> "No State shall. . . deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws."

STATUTES INVOLVED

§ 201(n) of the Federal Food, Drug and Cosmetic Act ("the Act"), 21 U.S.C. § 321(n); § 502(a) and (n) of the Act, 21 U.S.C. § 352(a) and (n); and § 505(a) and (d)(6) of the Act, 21 U.S.C. § 355(a) and (d)(6). These statutory provisions are set forth in Appendix B.

SUMMARY

This petition raises simple but compelling questions of federal law that affect the very framework of federal regulation of prescription drugs. The Kansas courts in this case premised their finding of liability and the concededly "enormous" punitive damages on Ortho's failure to warn physicians of the possibility that its prescription drug Ortho-Novum might cause a specific and exceedingly rare kidney disorder. Plaintiff's position that a warning about an unproven side effect was necessary conflicts with the plenary power of the federal FDA to supervise and approve the precise wording of advice to physicians concerning prescription drugs; indeed, critical to the Kansas Supreme Court's decision to uphold the punitive damage award was its conclusion that Ortho had omitted warnings about certain possible side effects *when the FDA had already determined that such a warning should not be made.* The Kansas ruling permits and encourages each of the fifty states to develop through imposition of punitive damages in personal injury litigation an extended list of warnings that must accompany the distribution of prescription drugs within that state—even if such required warnings conflict with one another and with a contrary determination by the FDA. It was precisely to avoid such "clutter," and the attendant risk that myriad additions would defeat the purpose of the prescribing instructions, that Congress established the FDA as the arbiter not only of what prescription drug warnings should contain but what they should not contain.

This case thus raises, in an industry where federal regulation is not only extensive but is deemed to be vital to the national health, the questions left open last Term in *Silkwood v. Kerr-McGee Corp.*, ____ U.S. ____, 104 S. Ct. 615 (1984), that is, whether an "award of punitive damages" is preempted because it "conflict[s] with the federal remedial scheme. . . ." 104 S. Ct. at 617. The Court should review this case, and the important federal constitutional issues of regulatory preemption it raises, before its emulation by the other states threatens chaos in the vitally important area of prescription drugs, with attendant risks to the national health.

STATEMENT OF THE CASE

HUS is a rare kidney disorder of unknown origin which occurs spontaneously in young women.[2] It is conceded that no one to this day knows whether oral contraceptives ("o.c.'s") in fact cause HUS. Many thousands of young women, however, ingest o.c.'s continuously over a period of years. Thus inevitably some women will have HUS or some other spontaneously occurring disorder coincidentally with their use of o.c.'s. At the time of Mrs. Wooderson's illness there had been only nineteen such cases (p. 1408). Mrs. Wooderson's was the first alleged incident of HUS in a woman taking Ortho-Novum ever reported to Ortho (p. 2243-45).

Under the common law of Kansas, as in virtually every other jurisdiction, liability for personal injuries caused by a prescription drug requires (a) proof that the seller of the prescription drug in the exercise of reasonable care should have placed in the prescribing instructions (sometimes referred to herein as the "package insert" or the "labeling" for the drug) a warning to prescribing physicians about the particular side effect, and

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2 HUS usually occurs in children (male or female) or young women (pp. 600, 935, 2356). Its symptoms are a significant drop in platelets (small disc-like particles in the blood which initiate blood clotting), insufficient kidney function (diagnosed by an abnormally high level of waste product—urea—found in the blood) and hemolytic anemia (rapid destruction of red blood cells) (pp. 597, 910).

(b) that had such a warning been given, the prescribing physician would have taken appropriate steps to avoid the injury.[3]

In this case, plaintiff never contended that liability for compensatory damages should be imposed on Ortho for failing to list HUS as an established adverse reaction, but rather for not listing it in prescribing instructions as a "suspected" adverse reaction for which "an association has neither been confirmed or refuted" (p. 1438-39). Plaintiff's expert on labeling gave the following argument for adding such a warning (p. 1440):

> "A. I think we've been through this once. I feel that as of 1976, there were nine reports with at least 19 patients, maybe as many as 23, that had been reported with one patient having a rechallenge. I think that is more than enough to list it as having occurred, and since it's such a serious effect, it's a matter of prudence when you have a potentially lethal effect of a drug, even though it's—*it's still at the suspicion stage and not confirmed with any statistical evaluation*. I think prudence demands that it be identified."[4]

In support of her claim for punitive damages, plaintiff relied in part on this same failure to warn of HUS as a possible but unconfirmed side effect. Equally, if not more important for purposes of this petition, plaintiff also relied upon the absence from Ortho's physician and patient labeling during the period 1970-74 of any discussion of the results of a British epide-

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3 *E.g., Lindquist v. Ayerst Laboratories, Inc.*, 227 Kan. 308, 607 P.2d 1339 (1980); *Stanback v. Parke, Davis & Co.*, 657 F.2d 642 (4th Cir. 1981); *Lindsay v. Ortho Pharmaceutical Corp.*, 637 F.2d 87, 91 (2d Cir. 1980) (o.c.). The physician functions as a "learned intermediary," and must exercise independent judgment free of manufacturer control in order to operate effectively. *E.g., Dyer v. Best Pharmacal*, 118 Ariz. 465, 577 P.2d 1084, 1088 (1978); *Stanback v. Parke, Davis & Co., supra*; Rheingold, *Products Liability—The Ethical Drug Manufacturer's Liability*, 18 Rutgers L. Rev. 947, 987 (1964).

4 Unless otherwise noted, emphasis herein has been added.

miological survey done in 1969. This survey purported to find a statistically significant association between thromboembolic diseases[5] and the estrogen content of o.c.'s (DX-AA).[6] The Opinion placed great reliance upon a "Dear Doctor" letter[7] sent by the FDA in January 1970 enclosing the uniform labeling promulgated by the FDA for *all* o.c. products (681 P.2d at 1062-63; a-104-6[8]) (PX-8F). This labeling was in effect from 1970 through 1974 (pp. 2063-65, 2129). As indicated in the Opinion (*id.*), this Dear Doctor letter was written primarily to bring the new uniform labeling for o.c.'s to the attention of prescribing physicians. However, while the letter did make reference to the British survey, the letter noted that its finding "has not been confirmed by other studies."

The major predicate in the Opinion for affirming the punitive damage award is that "Ortho played down the British report" and, further, "that Ortho continued to urge the use of its higher estrogen products" (*id.* at 1063; a-109), *i.e.*, urged the use of 1/80 as opposed to 1/50.[9] However, this British survey was limited to specific thromboembolic diseases and

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5 The thromboembolic diseases specifically discussed were thrombophlebitis, pulmonary embolism and strokes. Thrombophlebitis means inflammation and blockage of a vein by a blood clot. An embolus is a clot which has broken off and travelled downstream. A pulmonary embolus (or embolism) is a clot which has originated in a vein, travelled downstream into the right side of the heart and then pumped out into a lung bed. A stroke is usually caused by a thrombus or thromboembolus in a vessel supplying blood to the brain.

6 Most o.c.'s are combination drugs consisting of a relatively small amount of estrogen, a female hormone, and a relatively large amount of progestin, another female hormone.

7 A "Dear Doctor" letter is a mass mailing sent to all prescribing physicians.

8 Citations to "a-____" are to Appendix A.

9 The "80" and "50" refer to the amount of estrogen, in micrograms, in each pill.

had nothing whatsoever to do with acute kidney failure or HUS (pp. 2071-81; DX-AA). Moreover, it is likewise undisputed that Ortho analyzed this survey and concluded that it was methodologically flawed and statistically invalid (pp. 2096-97; pp. 2404-06).

In apparent awareness of these facts, the Kansas Supreme Court concluded that a drug manufacturer " 'may not ignore or discount that information [tending to show the existence of a certain side effect] in drafting its warning solely because it finds it to be unconvincing' [citation omitted]" (681 P.2d at 1044; a-67). This statement *omits the fact—critical to this petition—that the FDA had also found the British study to be unconvincing.*

Searle, another o.c. maker, wrote the FDA on April 30, 1970, referring to these same British findings and requesting permission to amend its labeling for o.c.'s to reflect these findings (R. L, p. 127). The FDA refused, informing Searle in writing that its "proposal has been carefully considered and found to be unacceptable" (pp. 565-87; DX-CC).

This action by the FDA *prohibiting* another drug company from amending its label to disclose the British study was critically relevant on the scope of Ortho's alleged duty to include warnings of the same study. But the trial court excluded this correspondence on the incredible ground that it was not relevant, and further found that it was not clear whether all of the underlying documents relating to this attempt at effecting a labeling change were produced (p. 2154-55). It was clear, however, that the request and rejection were produced at trial, and the trial court was made aware that the uniform labeling requirements for 1970-74 were never changed to reflect the survey. The Supreme Court of Kansas did not discuss the exclusion of this rejection by the FDA of Searle's request, and also ignored the FDA's dismissal of the 1969 survey in affirming the punitive damage award, which it conceded was "enormous" (681 P.2d at 1064; a-113).

In sum, the Kansas courts permitted a multi-million-dollar punitive damage award to be based in principal part on the

1969 British survey even though the documented evidence showed a) that the FDA regarded the 1969 British survey as unconfirmed and rejected a proposed labeling change to reflect the findings of this 1969 survey; b) Ortho's own contemporaneous analysis revealed this survey to be methodologically unsound, and c) the uniform labeling for o.c.'s, which the FDA promulgated, placed in effect in January 1970, and required to be maintained in effect during the years 1970-74, did not reflect the results of this survey. Thus, in this case Kansas has assessed punitive damages against Ortho to "punish" it under Kansas common law for failure to add a warning that the FDA had already found "unacceptable."[10]

The first federal question sought to be reviewed herein, the conflict between the FDA's policies and regulations and plaintiff's theory of Kansas law, was raised at trial, both during the testimony of Dr. Samuel A. Pasquale (pp. 2047, 2053, 2058-2062, 2163), and again when the trial court refused to consider proof that the estrogen-dose warnings plaintiff demanded were forbidden by the FDA (pp. 2140-2152). The issue was also presented in Ortho's Amended Motion for a New Trial, based on the newly discovered evidence that the FDA had in 1982 specifically disapproved warnings by Searle about HUS (R. IV, pp. 565-87). The trial court inexplicably ruled this new evidence was not relevant (R. XXXXII, p. 37). The argument was repeated on appeal to the Kansas Supreme Court (Br. of Appellant, pp. 11-21). The Court brushed off the plain proof that Ortho could not have warned about HUS without violating the FDA's directives with the incredible statement that the FDA's letter to Searle was not a "clear determination" that HUS did not merit a warning (p. 34-35). Although Ortho again pressed this federal question in its Motion for Rehearing to the Kansas Supreme Court, that motion was summarily denied (a-129).

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10 Significantly, the Kansas legislature has deferred entirely to the FDA in regard to labeling of prescription drugs marketed in the state. Kansas Food and Drug Statute, Kan. Stat. Ann. §§ 65-669(n), 65-669a (1983).

The question whether the Kansas court's refusal to apply that state's comparative negligence law deprived Ortho of due process has similarly been raised at every stage of the proceedings. *See* Ortho's Motion for Directed Verdict or New Trial (p. 15-22); Br. of Appellant, p. 27-31; Motion for Rehearing (p. 1-4). The claim was rejected at all levels.

THE REASONS FOR GRANTING THE WRIT

I. PUNITIVE DAMAGES ASSESSED AGAINST A DRUG COMPANY FOR COMPLYING WITH FEDERAL REGULATORY DIRECTIVES REGARDING LABELING CONTENT OF PRESCRIPTION DRUGS CONFLICTS WITH FEDERAL LAW AND STANDS AS AN OBSTACLE TO THE ACCOMPLISHMENT OF THE PURPOSES AND OBJECTIVES OF THE LABELING PROVISIONS OF THE FOOD, DRUG AND COSMETIC ACT

The decision below puts *all* marketers of prescription drugs in jeopardy of being assessed punitive damages by lay juries in products liability cases for distributing such drugs in accordance with the mandates of the FDA.

The assessment of punitive damages in products cases has become increasingly commonplace.[11] The rationale of *Roginsky v. Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967), which recognizes the bankruptcy specter inherent in permitting assessments of punitive damages for injuries for drug-induced side effects, has been effectively discarded.[12] One

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11 *See generally* Seltzer, *Punitive Damages in Mass Tort Litigation*, 52 Fordham L. Rev. 37-42 (1983); Wheeler, *The Constitutional Case for Reforming Punitive Damages*, 69 Va. L. Rev. 269, 271 (1983); Owen, *Problems in Assessing Punitive Damages Against Manufacturers of Defective Products*, 49 U. Chi. L. Rev. 1, 54 (1982).

12 Congress has expressly recognized the risk that businesses may face the choice between bankruptcy and discontinuation of a useful product line when faced with the prospect of large, cumulative awards when it drafted the

commentator notes that "whereas 25 years ago, the punitive damage case was a rarity, today it is an anomaly when one sees a complaint which does not seek punitive damages." Levit, *Punitive Damages: Yesterday, Today and Tomorrow*, 1980 Ins.L.J. 257, 259 (emphasis in original).

So far as we are aware, until recently, there had been only two punitive damage awards in prescription drug cases.[13] The law generally applied was that articulated in *G.D. Searle & Co. v. Superior Court*, 49 Cal.App.3d 22, 122 Cal. Rptr. 218 (3d Dist. 1975), which required proof of actual knowledge of a *proven* side effect coupled with failure to warn thereof. Now the proclivity for awarding punitive damages that has come to other areas of products liability is being transposed into the prescription drug liability area. These awards are being based as in this case on a lay jury's notions of gross negligence.[14] But whatever the desirability of awarding punitive damages in other kinds of products liability cases, these policy considerations clearly are inapplicable in the area of federally-supervised labeling of prescription drugs.[15]

Proposed Federal Products Liability Act. *See* S. Rep. No. 476, *Report of the Senate Comm. on Commerce, Science and Transportation on S. 44*, 98th Cong., 2d Sess., 8-9 (May 23, 1984). This proposed legislation (and a similar House bill, H.R. 2729), reflect extensive consideration of the threat posed to the American economy by out-of-control punitive awards. *Id.* at 13, 55-62.

13 One is *Toole v. Richardson-Merrell, Inc.*, 251 Cal. App.2d 689, 60 Cal. Rptr. 398, 418 (1st Dist. 1967) (punitive damages of $250,000), and the other was *Ostopowitz v. Wm. S. Merrell Co.*, No. 5879-1963 N.Y.L.J., Jan. 11, 1967, at 21, col. 3 (Sup. Ct. N.Y. Co. 1967) ($100,000 in punitive damages). Both of these, like *Roginsky*, involved MER 29, a withdrawn anti-cholesterol agent.

14 *See, e.g. Johnson v. Lederle Laboratories*, No. 81-C-2470 (Sedgwick Co., Kan. Dist. Ct., June 15, 1984) ($8 million in punitive damages in case involving oral vaccine); *Batteast v. Wyeth Laboratories*, No. 77L.12460 (Cook Co., Ill., Cir. Ct. July 1984) ($13 million in punitive damages in case involving prescription drug, aminophylline.

15 *See generally Roginsky v. Richardson-Merrell, supra*; *see also* Seltzer, *Punitive Damages, supra*, at 48-55; Owen, *Problems in Assessing Punitive Damages, supra*, at 27.

Prescription drugs are by definition inherently dangerous. They are nonetheless prescribed hundreds of millions of times in any given year, ingested even more often, and, given their necessarily powerful effects, unavoidably result in literally thousands of adverse reactions on a daily basis. That is why, as a matter of federal law, they are sold only under the prescription and continuing supervision of a duly licensed expert, the physician. To implement this law, Congress has delegated to the FDA the administrative function of assuring that these experts receive meaningful information in the prescribing instructions to enable them to prescribe and supervise the drug therapy as safely as possible. 21 U.S.C. § 352(n). The FDA has developed detailed procedural and substantive regulations to supervise the content of information provided to prescribing physicians and imposes sanctions for failures to comply with these procedures.

The decision in this case severely undermines the authority of the FDA, and puts every drug manufacturer and prescribing physician at risk if he complies with the FDA's standards. By its insistence that o.c. labeling set forth every possible side effect even where the FDA has determined that such a warning was inappropriate, Kansas has precipitated a fundamental collision with federal law.

Thus, this case presents the very fact situation which this Court in *Silkwood v. Kerr-McGee Corp., supra*, implicitly recognized creates a preemption by federal regulation. In *Silkwood*, this Court delineated two areas where preemption occurs even though Congress has not expressed an intent to occupy the entire field. "[S]tate law . . . is preempted to the extent it actually conflicts with federal law, that is, when it is impossible to comply with both state and federal law"; and preemption also occurs "where the state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress." *Id.* at 621.[16] The regulation of label-

16 *See also Jones v. Rath Packing Co.*, 430 U.S. 519, 540 (1977) (holding of preemption inescapable where it is impossible "to comply with state law without triggering federal enforcement actions").

ing content by the Kansas courts through imposition of punitive damages even though the FDA had authorized the labeling content at issue, is preempted by the Act under both tests.

A. The Direct Conflict Between the Kansas Punitive Damage Award and The Specific Actions Taken By the FDA in Regulating Prescription Drug Labeling

As appears more fully below, the factual situation here is one which the majority in *Silkwood* implicitly recognized as creating a direct conflict between state and federal law. The *Silkwood* majority reaffirmed the basic proposition, recognized in prior decisions of this Court, that punitive damages are regulatory, rather than compensatory in purpose:

> " '[R]egulation can be as effectively asserted through an award of damages as through some form of preventive relief.' "

104 S.Ct. at 622, quoting *San Diego Building Trades Council v. Garmon*, 359 U.S. 236 (1959).[17] In *Silkwood* this Court agreed with the following analysis by the District Court in denying the motion by Kerr-McGee for judgment n.o.v.:

> "The [district] court noted that Kerr-McGee 'had a duty under part 20 of Title 10 of the Code of Federal Regulations to maintain the release of radiation '*as low as reasonably achievable*.' Compliance with this standard cannot be demonstrated merely through control of escaped plutonium within any absolute amount.' . . . Therefore, the court concluded, it is not 'inconsistent [with any congressional design] to impose punitive damages for the escape of plutonium caused by grossly negligent, reckless and willful conduct.' " *Id.* at 620.

In other words, the punitive award in *Silkwood* enforced a standard under Oklahoma law that was identical to one es-

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17 *See also Smith v. Wade*, 461 U.S. 30, 103 S. Ct. 1625, 1636 (1983) (deterrence of punished conduct is "primary purpose" of punitive damages); *Gertz v. Robert Welch, Inc.*, 418 U.S. 323, 348-50 (1974) (punitive damages are "civil fines" which serve no compensatory purpose).

tablished by the federal agency—one designed, understandably enough, to keep radiation levels "as low as reasonably achievable." The conclusion of the *Silkwood* jury that Kerr-McGee in fact violated this standard, and did so in reckless disregard of public safety, did not conflict with the standard announced by the federal regulator, the NRC. The majority in *Silkwood* therefore concluded that there was no "irreconcilable conflict between the federal and state standards" and that "the imposition of a state standard in a damages action would [not] frustrate the objectives of the federal law." *Id.* at 626.

In this case, however, the state court jury in effect regulated the content of prescription drug labeling under standards diametrically opposed to those of the FDA. The Supreme Court of Kansas approved the trial court's charge to the jury that Ortho was "presumed to know of *all* potential dangers of a drug which *could* have been discovered" and had the obligation to warn of any such danger which "is serious" (R. II, p. 300). It further told the jury that while compliance with the applicable FDA regulations may be considered as evidence of due care, such compliance "does not relieve a manufacturer of the duty set forth in these [jury] instructions." The jury was further told that if Ortho was "wanton" in violating this duty created *under Kansas law* they should award as punitive damages such sum as "will serve to punish defendant, Ortho Pharmaceutical Corporation, and to deter others from like conduct." A wanton act was defined as one done with "a realization of the imminence of danger and a reckless disregard or complete indifference to the probable consequences of the act" (R. II, p. 312).

The foregoing instructions virtually compelled an award of punitive damages under the facts of this case—as they would in many instances of distribution of prescription drugs with federally approved warnings. It was not disputed that HUS is "serious" or that Ortho knew of occasional anecdotal reports of HUS among users of other types of o.c.'s prior to Mrs. Wooderson's kidney failure and that after investigation of her kidney failure, Ortho decided not to add a warning to its physician labeling that HUS was an unconfirmed but possible rare adverse reaction. Nor did Ortho contest that it did not

alter its patient warnings—which had been mandated and approved by the FDA—by adding such a warning. Thus, the jury could have concluded *under the instructions* that Ortho deliberately violated a duty under Kansas law to warn both Mrs. Wooderson's doctors and the patient herself of all potential or possible serious side effects of the drug, including HUS and acute kidney failure.

The Supreme Court of Kansas affirmed the award of punitive damages on the ground that Ortho "is under a duty [under Kansas law] to make known to the medical profession, or at least those physicians who are prescribing that drug, any of the dangerous side effects of which it knows *or has reason to know*" (emphasis in original) (681 P.2d at 1062; a-101-2), and concluded that punitive damages were properly awarded in an amount of $2.75 million because in its view the jury "could have found" that Ortho in issuing its labeling without these warnings "was grossly negligent and recklessly indifferent to the rights of others, including this plaintiff" (681 P.2d at 1064; a-112).

Punishing Ortho for violating these state-imposed duties to warn directly conflicts with federal law in a number of ways. First of all, the requirement that Ortho *must* include warnings of all suspected, but unconfirmed, serious side effects in its labeling flies in the face of FDA regulations.

Turning to the physician labeling, the FDA does not, contrary to the trial court's charge and the implicit assumption of the Supreme Court of Kansas, merely set *minimum* standards for the content of the labeling, onto which the drug manufacturer may add more warnings or other refinements as it sees fit. Section 502(a) of the Act provides that "a drug . . . shall be deemed to be misbranded (a) if its labeling is false or misleading in *any* particular." 21 U.S.C. § 352(a). With respect to prescription drug labeling, the Act directs the Commissioner to issue regulations which provide "information in brief summary relating to side effects, contraindications and effectiveness" of the drug. 21 U.S.C. § 352(n). In a 1972 preamble statement, the Commissioner of the FDA offered this formal interpretation of the Act:

> "In approving the labeling the Food and Drug Administration must determine both that the content is entirely truthful, and that it omits *no* information pertinent to the safe and effective prescribing of the drug by the physician. Congress intended the labeling to be a full, complete, honest, and accurate appraisal of the important facts that have *reliably* been proved about the drug."[18]

As part of its duty to see that the labeling "omits no information pertinent to the safe and effective use of the drug by the physician", the FDA not only regulates what is contained in the package insert, but more importantly what is *not* to be in the package insert. It determined to do so following an injunction obtained by an independent group of physicians prohibiting the FDA from requiring a warning in the labeling for certain antidiabetic drugs against alleged but unproven cardiovascular adverse reactions. *Bradley v. Weinberger*, 483 F.2d 410 (1st Cir. 1973). The proposed labeling was rejected by the FDA for failure to comply with a regulation which at that time required the disclosure of the "existence of a difference of opinion" as to an alleged adverse reaction "if there is a material weight of opinion" to the contrary.

Following this decision, the FDA revised its basic labeling regulation to provide in pertinent part (21 C.F.R. § 1.21):

> "(a) Labeling of a food, drug, device, or cosmetic shall be deemed to be misleading if it fails to reveal facts that are. . . material. . . .
>
> * * * *

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18 37 Fed.Reg. 16503, 16504 (1972). These preambles are advisory opinions of the FDA, intended to let manufacturers know in advance whether their labeling will be violative of the Act, or is likely to meet with FDA approval. 21 C.F.R. § 10.85(d)(1). As such they are interpretations "of a statute by those charged with their execution" which "should be followed unless there are compelling indications that [they are] wrong, especially when Congress has refused to alter the administrative construction." *Red Lion Broadcasting Co. v. FCC*, 395 U.S. 367, 381 (1969); *Stevens v. Commissioner*, 452 F.2d 741, 746 (9th Cir. 1971).

(c) Paragraph (a) of this section does *not*:

(1) Permit a statement of differences of opinion with respect to warnings (including contraindications, precautions, adverse reactions, and other information relating to possible product hazards) required in labeling for food, drugs, devices, or cosmetics under the act."

The FDA explained the purpose of this revision as follows:

"It is . . . apparent that there are very few statements in prescription drug labeling on which some controversy could not be found within the medical profession. Not infrequently, there are several points of view on a single issue. To permit or require statements of conflicting opinion on all of these matters would destroy the present usefulness of prescription drug labeling." 39 Fed. Reg. 33229, 33232 (1974).

The Commissioner went on to state that:

". . . if the Congress were to provide that a representation, about the correctness of which qualified opinion differed, would be misleading if the jury agreed with the experts holding one view but not misleading if the jury agreed with the experts holding the other view, it is apparent that the manufacturer would be unable to tell in advance whether his labeling violated the statute [and that it would be] undesirable to permit misleading claims to be made simply because a few experts can be found on the occasion of a trial to support them". *Id.* at 33230.

The Commissioner concluded:

"The presence of unsubstantiated medical opinion in drug labeling would be misleading within the meaning of sections 502(a) and 201(n) of the act." *Id.* at 33232.

In a further contemporaneous explanation for this change, Dr. Temple, special assistant to the Director of the Bureau of

Drugs of the FDA, in *Legal Implications of the Package Insert*, 58 Med. Clin. No. Amer. 1151, 1155 (1974), stated:

> "It is important to recognize what the package insert is and also to recognize what it is not. The most important feature of the package insert, the one that distinguishes it from other sources of information and makes possible its use as an *authoritative* reference source, is that its content must be based on substantial evidence. The labeling cannot simultaneously meet this requirement and be fully up to date. It cannot be both *authoritative* and *avant-garde*."

The Commissioner has made the same point repeatedly. For example he stated that the "statutory scheme for drug labeling is intended to provide physicians, in straightforward and concise terms, with the information they need to prescribe a drug under conditions that maximize the drug's effectiveness and minimize its risks." 44 Fed. Reg. 37434, 37436, ¶ 8 (1979).

Elsewhere he has stated:

> "Physicians clearly have access to new information on drugs through the medical literature, scientific meetings, postgraduate courses, and professional contacts with colleagues. The package insert is not intended under the law to serve as a totally current repository of all such information. It is intended instead to be an *authoritative* document which contains only those indications and usages based upon *substantial* evidence of safety and effectiveness." 40 Fed. Reg. 15392, 15394 (1975).

1. The Conflict Over Inclusion of an HUS Warning in the 1976 Labeling

These regulations and constructions demonstrate that the FDA's standards for approving labeling regulate what the labeling should *not* contain as well as what it should contain. In the discharge of this duty to regulate what should *not* be contained in the package insert, the FDA has decided that package inserts for o.c.'s should not be loaded up with warnings about speculative side effects, such as the HUS warning. This is precisely what it determined in rejecting the changes

proposed by Searle, discussed above. These changes, including the HUS addition, were obviously designed for products liability litigation to minimize or preclude exactly the kind of liability visited upon Ortho in this case; yet they were rejected by the FDA.

Stated another way, under the FDA's view of its role in regulating content of labeling, the issue is not whether this suspected but unconfirmed possible side effect "merits a warning", but rather whether it undermines the objectives of the Act to include such a warning. Under the established law and regulations requiring the FDA to exclude unnecessary information from the labeling, this explicit determination by the FDA—more than six years after Mrs. Wooderson's injury—that an HUS warning should not be included, coupled with its approval of the 1976 labeling without an HUS warning with full knowledge of the anecdotal reports of HUS coincident with o.c. use (pp. 2349-52), precludes Kansas from punishing Ortho for not loading up its labeling with information about this unconfirmed, possible side effect.

2. The Conflict Over Inclusion in the Uniform Labeling of An Alleged Estrogen Dose Relationship to Thromboembolic Disease

Kansas also punished Ortho for compliance with the uniform labeling promulgated by the FDA in omitting a reference to the findings of the British study during 1970-1974. In doing so, it created an even sharper conflict between Kansas' common law regulation and that of the FDA. In promulgating this uniform labeling, the FDA determined that it was in the best interest of the public health and welfare to require all o.c. makers to use this labeling and by telegram in January 1970 advised o.c. marketers "that use of labeling containing uniform portion other than *exactly* that in our letter of November 14, 1969, may be basis for regulatory action."

As the FDA pointed out in its "Dear Doctor" letter of January 1970 enclosing this uniform labeling, the labeling was drafted by the Obstetrics and Gynecology Advisory Committee to the FDA (PX-8F), one of several advisory committees which advise the FDA on labeling content for various classes of

drugs.[19] As noted, in promulgating this labeling drafted by the Obstetrics and Gynecology Advisory Committee, the FDA also explicitly referred to the British survey on the alleged estrogen dose relationship to thromboembolic disease in its January 1970 Dear Doctor letter enclosing the labeling. Yet it determined *not* to include the results of that study in such labeling, and forbade Searle to change its labeling to reflect this survey.

3. The Conflict Over the Content of Patient Labeling

The trial court in effect charged the jury that Ortho also had a duty to warn Mrs. Wooderson directly of potential serious side effects. Although the trial court recognized the established law that a drug company had no common law duty to issue warnings to the patient, he nevertheless charged the jury as follows:

> "If the manufacturer *chooses* to communicate directly with the consumer, it has a duty not to mislead the consumer so as to unduly minimize or nullify warnings which have been given to the physician or consumer" (R. II, p. 303).

The Supreme Court of Kansas sought to neutralize the patent error in creating a duty for the drug manufacturer to warn the patient directly by stating (681 P.2d at 1057; a-77):

> "We do not need to determine, in this case, what duty, if any, such a manufacturer [of prescription drugs] has to warn the ultimate consumer, the patient. Here, neither

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19 To assure that the FDA's required labeling is as unbiased and effective as possible, the agency appoints a committee of qualified experts to recommend the labeling for each of nineteen classes of drugs, e.g. anti-hypertensive, anti-inflammatory. "The committees are composed of members of the scientific and medical communities who are engaged in research and clinical practice. . . . A committee may be asked to resolve a question arising at any stage of the review process, but its activities primarily revolve around the review of NDAs and clinical guidelines." Dorsen, "Final Report of the Review Panel on New Drug Regulation" (1977), reprinted in *The Drug Regulation Reform Act of 1978: Hearings on H.R. 11611 Before The Subcommittee on Health and Environment of the Committee on Interstate and Foreign Commerce*, 95th Cong., 2d Sess. at 599 (1978).

> was warned by Ortho, but Ortho's failure to warn the physician [of HUS] is sufficient to sustain the finding of negligence or breach of duty against it in this case."

This reasoning ignores the urging by Mrs. Wooderson's attorney of this breach of this non-existent duty as a basis for imposing punitive damages on his summation (pp. 2956, 3082).[20] There is no assurance that the punitive award was not based in whole or in part on the erroneous argument that Ortho breached some duty to warn the patient. *United New York and New Jersey Sandy Hook Pilot Ass'n v. Halecki*, 358 U.S. 613, 619 (1959), *Bose Corp. v. Consumers Union*, ____ U.S. ____, 104 S.Ct. 1949, 1969 n.2 (1984) (dissenting opinion). This final regulatory violation for which Ortho may well have been punished by the jury—namely, allegedly inadequate warnings to the patient—also sharply conflicts with federal law.

In June 1970, the FDA mandated that a brief warning be placed on the flap of o.c. drug dispensers warning users that "the most serious known side effect of oral contraceptives is abnormal blood clotting which can be fatal", and alerting them to the existence of a patient booklet. 35 Fed. Reg. 9001 (1970). The FDA further required that this patient booklet contain twelve, and *only* twelve pieces of information, and that it be made available to every patient through the prescribing physician. *Id.* at 9003.[21] Since the FDA did not permit o.c.

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20 This reasoning also ignores the testimony of Mrs. Wooderson that although she had been warned that o.c.'s exposed her to death through abnormal blood clotting, e.g., heart attacks and strokes, she was misled because there was no reference given to her regarding kidney failure and that she would not have taken the drug if she knew it might cause kidney failure (pp. 1216, 1276).

21 Thus, contrary to the trial court's charge, Ortho did not "choose" to communicate directly with the patient. Rather, in compliance with FDA regulations Ortho duly attached to the monthly drug container and included in the patient booklet the warning containing the specific language mandated by the FDA. The sole statement in the brochure not explicitly required by the terms of the FDA regulations, is this foreword (DX-B):

> "The inclusion of the following information regarding the effectiveness and known hazards of oral contraceptives is required by the Food and Drug Administration."

manufacturers to discuss the British study in the labeling directed to physicians, it necessarily would not have allowed a discussion of the arcane question of a possible relationship of estrogen dose to thromboembolic problems to be included in these simplified warnings designed for lay persons.

B. THE REGULATION BY KANSAS OF PRESCRIPTION DRUG LABELING AS ADMINISTERED IN THIS CASE STANDS AS AN OBSTACLE TO THE ACCOMPLISHMENT OF THE PURPOSES AND OBJECTIVES OF CONGRESS

The Kansas court here indulged in a presumption that had a more detailed warning been given to Mrs. Wooderson's prescribing doctors, such a warning would have been heeded and have prevented the injury.[22] This petition does not seek a review of the use of this presumption to *compensate* victims of injuries that are found to be drug related. Use of this fiction—that warnings more elaborate than those approved by the FDA would have avoided the injury—to impose *punitive* damages, however, threatens the very purpose of the FDA regulatory function over labeling, and should be reviewed.

What the Kansas courts did in this case by imposing enormous punitive damages was to require Ortho to load up the package insert with additional warnings about specific disorders which are at times coincidental with the use of the drug. The FDA, however, has determined that such informational clutter is actually destructive of the important function of the package insert. The FDA has categorically rejected the argument "that undesirable effects 'coincidental' with the use of the drug should be included in the definition [of an adverse reaction] to protect manufacturers from product liability actions." 44 Fed. Reg. 37434 (1979). In this 1979 analysis, the FDA reiterated its philosophy in rejecting the approach to labeling used by the First Circuit in *Bradley v. Weinberger, supra*:

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22 Primarily because a more detailed warning would in virtually all cases have made no difference to the prescribing doctor, this presumption is sometimes used in drug cases as a basis for imposing liability. *See, e.g., Sterling Drug v. Yarrow*, 408 F.2d 978 (8th Cir. 1969).

> "One comment suggested that disclosure of significant medical and scientific controversy surrounding a reported adverse reaction be permitted. The Commissioner advises that inclusion in drug labeling of medical or scientific controversy concerning labeling statements would be highly confusing, and thus misleading, in violation of section 502(a) of the act." 44 Fed. Reg. at 37452.

Consequently, federal law requires that labeling be "based on data derived from human experience," 21 C.F.R. § 201.56(c), and that it advise of "known hazards and not theoretical possibilities." 21 C.F.R. § 201.57(d). *See also* 21 C.F.R. § 201.56(a) (labeling must be based on "scientific information"). The FDA has noted:

> "Labeling is not intended to be a dispositive treatise of all possible data and information about a drug. It is intended instead to advise about potential hazards and to convey documented statements concerning safety and effectiveness. The act permits labeling statements with respect to safety only if they are supported by scientific evidence.
>
> "The Commissioner concludes that drug labeling should include a contraindication only when reasonable evidence exists indicating an association between the drug and a hazard. *The Commissioner believes that including theoretical hazards as contraindications in drug labeling would cause that very important section of the labeling to lose its significance.*" 44 Fed. Reg. 37434 at 37441, 37446-47.

As stated by the Supreme Court of California in the recently decided prescription drug case *Finn v. G.D. Searle & Co.*, 35 Cal.3d 691, 200 Cal. Rptr. 870, 876, 677 P.2d 1147 (1984):

> " 'If we overuse warnings, we invite mass consumer disregard and ultimate contempt for the warning process.' (Twerski et al., supra, 61 Cornell L. Rev. at p. 521.) Moreover, both common sense and experience suggest that if every report of a possible risk, no matter how speculative, conjectural, or tentative, imposed an affirma-

> tive duty to give some warning, a manufacturer would be required to inundate physicians indiscriminately with notice of any and every hint of danger, thereby inevitably diluting the force of any specific warning given. (See Twerski, *From Risk-Utility to Consumer Expectations: Enhancing the Role of Judicial Screening in Product Liability Litigation*, 11 Hofstra L.Rev. (Spring 1983) 861, 932-935; *Thompson v. County of Alameda* (1980) 27 Cal.3d 741, 755)."

Congress has delegated the ultimate authority over labeling to the Secretary of Health and Human Services. 21 U.S.C. §§ 352, 355, 371(a). This authority has been redelegated by the Secretary to the FDA, 21 C.F.R. § 5.10(a)(1), and the FDA has proceeded to exercise that authority, 21 C.F.R § 314. Indeed, 21 C.F.R. § 10.25(b) provides that a court should in the first instance defer to the FDA's expertise. It gives the FDA "primary jurisdiction to make the initial determination on issues within its statutory mandate. . . ." This Court, in recognizing this primary jurisdiction of the FDA, stated in *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 654 (1973):

> " 'Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background.'. . . Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand."

The precise issue raised here is whether Kansas should be allowed to overrule the FDA's determination that dissertations about possible side effects that may be encountered during drug therapy and diagnosis thereof are not appropriate subjects for labeling. Kansas in effect has arrogated to itself this primary jurisdiction, and has determined to impose its views about what labeling for prescription drugs sold in interstate commerce should contain. Its direction that the labeling must contain such clutter—at risk of concededly "enormous" punitive damages—is at direct odds with the purpose of the FDA, stated time and time again, to have simple, precise and authoritative prescribing instructions.

The FDA has also rejected the argument, used by plaintiff here and adopted by the Kansas court, that the package insert should have instructed the prescribing physician how to detect and diagnosis HUS or other types of acute kidney failure:

> "Labeling is not intended to be a dispositive treatise of all possible data and information about a drug. . . . Labeling. . . cannot be transformed into the primary source of such information if it is to continue to be as concise and clear as possible." 44 Fed. Reg. 37434, 37441.

The FDA explained:

> "It [labeling] is intended instead to advise about potential hazards and to convey *documented* statements concerning safety and effectiveness." *Id.*

Overloading the package insert with all sorts of warnings of marginal or debatable relevance would truly destroy the usefulness of the package insert.

The 1984 Physicians Desk Reference Manual (the "PDR"), which contains verbatim the text of FDA-authorized warnings on most drugs, is already over 3,000 pages in length. Kansas' regulation would require that the prescribing instructions for each of the hundreds of drugs contain extended information about all serious disorders coincident with the use of the drug and that they also contain medical educational material on how to diagnose and treat such effects. This would literally require a PDR of tens of thousands of pages. The prescribing instructions included in the PDR are communications intended to convey *authoritative* information to busy professionals and as such they must, if they are to perform their function, presuppose the expertise required of a trained and licensed physician. Plainly put, prescribing instructions cannot act as surrogates for teaching someone how to practice medicine; Kansas' attempt to force FDA-mandated instructions to perform that role conflicts with the FDA's exercise of its own powers.

The actions by Kansas in assuming this regulatory role over drug labeling are analogous to that of the State of Minnesota in requiring labeling on aerosol containers in addition to that required by the FDA, which was struck down in *Cosmetic,*

Toiletry & Fragrance Ass'n v. Minnesota, 440 F. Supp. 1216 (D. Minn. 1977), *aff'd on opinion below*, 575 F.2d 1256 (8th Cir. 1978). The court rejected Minnesota's argument that this additional labeling was not "an obstacle to the accomplishment and execution of the full purpose and objective of Congress". *Id.* at 1224. It noted that preemption problems under the Act do not normally arise until the FDA has acted "with respect to a *specific* regulatory goal" and concluded that the FDA in this instance did so, stating:

> "[W]hen federal agencies have perceived a specific risk and have required labeling to alleviate that risk, the court feels that a state's freedom to require other than identical labeling with respect to that risk is precluded." *Id.* at 1223.

The court's reasoning as to why the action by the State of Minnesota frustrated the labeling role of the FDA is particularly pertinent here:

> "[W]here goods are distributed on a national level, a subordinate unit of the government should not be able to require that an interstate producer create special packaging or manufacture a special product for a limited distribution area *once* the federal government has acted with regard to the interest sought to be furthered by the subordinate entity's action." *Id.* at 1223-24.

The proper labeling of prescription drugs is a matter of far more serious concern than labeling for aerosol containers. Yet, unless this Court reaffirms the primacy of the FDA's determination of what is misleading or inadequate labeling, manufacturers who distribute in states which do not follow the FDA standards continue to face the risk of astronomic punitive awards. Thus, a national manufacturer could not have complied with both the mandates of the FDA and the courts of Kansas in its labeling at the same time.

Moreover, the decision of the Kansas court invites other states to force manufacturers to make similar warnings every time the facts developed in a litigated personal injury case suggest to a lay jury the advisability of such a warning—even

when the warning has been found unnecessary or even unlawful by the FDA or another state. It was precisely to avoid such conflicts that the Supremacy Clause exists and the doctrine of pre-emption has developed. The rejection of their precepts by the Kansas Supreme Court should be reviewed.

II. STRIPPING ORTHO OF ITS STATUTORY RIGHT TO OBTAIN ADJUDICATION OF THE COMPARATIVE FAULT OF THE PLAINTIFF AND THE PHYSICIANS ON THE GROUNDS THAT THERE WAS NO EVIDENCE OF CAUSAL NEGLIGENCE DEPRIVES ORTHO OF EQUAL PROTECTION AND DUE PROCESS OF LAW

Fundamental to the Anglo-American adversary system is the right to be heard and present evidence on an issue of fact. As Chief Justice Schroeder pointed out in his dissent in the Kansas Supreme Court (681 P.2d at 1065-66; a-121-26), Ortho supposedly had the right under Kansas law, Kan. Stat. Ann. § 60-258a, to obtain an adjudication "of proportionate fault of *all* parties to the occurrence." *Brown v. Keill*, 224 Kan. 195, 580 P.2d 867 (1978). Though it is not clear from the Opinion, the Kansas Supreme Court seems to have affirmed the trial court's apparent finding that Ortho waived its right to put in its own evidence of negligence of the physicians, and that thus there was no issue of their comparative fault to submit to the jury (681 P.2d at 1059-60; a-86-94). It also ruled that there was no evidence tending to show negligence on the part of the plaintiff (*id.* at 1060; a-95). Both of these rulings are transparent pretexts for denying Ortho its right of apportionment and cannot be squared with the equal protection and due process clauses.

Turning first to the plaintiff's comparative fault, the Court ruled (*id.*):

> "There is no testimony, medical or otherwise, which suggests that this failure to go to the hospital on June 25 caused or contributed to her injuries or that her condition was reversible on June 25."

This is not accurate. Plaintiff's case on failure to warn was predicated on the undisputed fact that successful treatment of any acute kidney failure, including HUS, depends upon its being treated almost immediately after it develops. Her experts so testified (pp. 948-49; R. LXXIII, p. 180), and the Kansas Supreme Court actually faulted Ortho because it "had not alerted them [the physicians]" of the need for immediate diagnosis and treatment (681 P.2d at 1060; a-93). Had the plaintiff gone to the hospital as directed she would have been worked up and her uremia (high urea blood levels) been detected. To quote Justice Schroeder, "to declare [on this record] as a matter of law that there was no evidence . . . on the issue of plaintiff's contributory negligence is presumptuous and speculative" (681 P.2d at 1066; a-126).

What is accurate is that the trial court did affirmatively prevent Ortho from questioning its own experts as well as those of the plaintiff and plaintiff herself on the comparative fault inherent in this three-day delay in seeking treatment (pp. 494-97, 1205).

Depriving Ortho of its statutory right to apportionment because the trial court precluded it from arguing plaintiff's comparative fault is like fashioning a rule of law which presumes a person to be guilty unless he argues that he did not commit the crime and then affirming his conviction after the trial court has prevented him from making the argument. It requires no citation of authorities other than the Constitution itself to demonstrate the unfairness inherent in such a result. The Kansas court never addresses the trial court's explicit rulings precluding Ortho from arguing plaintiff's fault. Such a discussion cannot be undertaken without exposing the unconstitutional unfairness of this result.

Turning to the issue of the physicians' comparative fault in not making a prompt diagnosis, the Kansas Court seems to find a waiver by Ortho of this issue in a pre-trial conference, but it never comes to grips with Ortho's explicit reservation in the order entered in that conference of its right to put on evidence designated by the plaintiff showing the negligence of the prescribing and treating doctors. (R. I, p.7). Plaintiff

designated the deposition of her expert and his report as exhibits. Those exhibits in and of themselves contain a plethora of evidence tending to show the negligence of the doctors (R. II, pp. 179-80; R. LXXII, pp. 141-43). Thus, the Court's affirmance on the ground that "[t]here was *no* evidence, expert or otherwise, of actual, causal negligence on the part of [the treating doctors]" (681 P.2d at 1060; a-94) is subject to the same constitutional infirmity as its ruling with respect to the lack of such evidence on the part of the plaintiff herself.

The Opinion also implies that in any event there was no legitimate issue of fact with respect to the doctors' negligence. Again, the undisputed facts testified to by plaintiff's own experts are (1) that successful treatment of any acute kidney failure, regardless of cause, depends upon diagnosis and treatment as soon as possible (pp. 948-49; R. LXXIII, p. 180); (2) that Mrs. Wooderson presented with the classic symptoms of acute kidney failure; and (3) that her physicians did not make a prompt diagnosis on their own. Thus, the Court's conclusion that "plaintiff offered no evidence of causal negligence on the part of the physicians" (681 P.2d at 1060; a-94) is inaccurate. The plaintiff may not have offered the evidence for that purpose but the evidence was clearly in the record, as the dissent recognized (681 P.2d at 1065-66; a-118-19, a-125). Ortho had the constitutional right to argue this point to the jury, and the trial court precluded it from doing so (pp. 1200-07):

> "You may not by inference or otherwise attempt to draw any conclusions by the witness' answers or by your questions that the doctors are guilty of malpractice or that they were ever in this lawsuit."

CONCLUSION

For the reasons set forth above, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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84-290

No. 84-____

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CLERK

IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

—v.—

CAROL LYNN WOODERSON,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF KANSAS

APPENDICES

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APPENDIX B

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APPENDIX A

No. 55,655

CAROL LYNN WOODERSON,
Appellee,

v.

ORTHO PHARMACEUTICAL CORPORATION,
Appellant.

SYLLABUS BY THE COURT

1.

When a verdict is attacked for insufficiency of the evidence, the duty of the appellate court extends only to a search of the record for the purpose of determining whether there is any competent substantial evidence to support the findings. The appellate court will not weigh the evidence or pass upon the credibility of the witnesses. Under

these circumstances, the reviewing court must review the evidence in the light most favorable to the party prevailing below.

2.

"Substantial evidence" is defined as evidence which possesses both relevance and substance and which furnishes a substantial basis of fact from which the issues can reasonably be resolved.

3.

The manufacturer of ethical or prescription drugs has a duty to give timely and adequate warnings to the medical profession of any dangerous side effects

produced by its drugs of which it knows, or has reason to know.

4.

The duty to warn must be commensurate with the seriousness of the danger. The greater the danger, the greater the duty.

5.

Although the duty of the ethical drug manufacturer is ordinarily to warn the doctor rather than the patient, the manufacturer is directly liable to the patient for a breach of such duty.

6.

In the case of drug manufacturers, the standard of constructive knowledge is that of an expert in that particular field.

7.

Because a manufacturer cannot be required to warn of a risk unknown to science, the knowledge chargeable to the manufacturer of an ethical drug must be limited to that of the period during which the plaintiff was using the product in question.

8.

The duty to warn is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge relevant to its products as gained through research, adverse reaction reports, scientific literature, and other available methods.

9.

An adequate warning is one reasonable under the circumstances.

10.

Where scientific or medical evidence exists tending to show that a certain

danger is associated with use of a drug, the manufacturer may not ignore or discount that information in drafting its warning solely because it finds it to be unconvincing.

11.

There is a presumption that an adequate warning would be heeded. This operates to the benefit of a manufacturer where adequate warnings are in fact given. Where warnings are inadequate, however, the presumption is in essence a presumption of causation.

12.

What a doctor might or might not

have done had he or she been adequately warned is not an element plaintiff must prove as a part of his or her case.

13.

The intent and purpose of the legislature in adopting K.S.A. 60-258a is to impose individual liability for damages based on the proportionate fault of all of the parties to an occurrence which gave rise to the injuries and damages, whether or not those persons are joined as parties to the action.

14.

A party who seeks to reduce his percentage of fault by comparing the

fault of another party has the burden of proving the other party's fault by a preponderance of the evidence.

15.

Where there is no evidence of causal negligence on the part of a person, the question of that person's negligence need not be submitted to the jury.

16.

Punitive damages are permitted whenever the elements of fraud, malice, gross negligence, or oppression mingle in the controversy.

17.

Punitive damages are allowed not because of any special merit in the injured party's case, but are imposed to punish the wrongdoer for malicious, vindictive or willful and wanton invasion of the injured party's rights, the purpose being to restrain and deter others from the commission of like wrongs.

Appeal from Sedgwick District Court; DAVID P. CALVERT, judge. Opinion filed April 27, 1984. Affirmed.

David F. Dobbins, of Patterson, Belknap, Webb & Tyler, of New York, New York, argued the cause, and Donald R.

Newkirk, of Fleeson, Gooing, Coulson & Kitch, of Wichita, was on the briefs for appellant.

Gerald L. Michaud, of Michaud, Cordry, Michaud, Hutton & Hutton, of Wichita, argued the cause, and Andrew H. Hutton and Dwight A. Corrin, of the same firm, were with him on the brief for appellee.

The opinion of the court was delivered by

MILLER, J.: Plaintiff, Carol Lynn Wooderson, brought this action in the District Court of Sedgwick County for damages for personal injuries which she claims resulted from her ingestion, over a period of years, of the oral contra-

ceptive Ortho-Novum 1/80, manufactured by the defendant, Ortho Pharmaceutical Corporation (Ortho). At the conclusion of a six-week trial, the jury returned a verdict and the court entered judgment for plaintiff and against Ortho for actual damages of $2,000,000 and punitive damages of $2,750,000. Ortho appeals. The primary issues are whether there was sufficient competent evidence to support the verdict, and whether the trial court properly submitted the matter of punitive damages to the jury. Other issues will be stated in the opinion.

Carol Lynn Wooderson consulted Dr. Richard L. Hermes of Lawrence, Kansas, a physician specializing in obstetrics and gynecology, in the fall of 1972.

She was planning to be married and wanted some method of contraception. Dr. Hermes prescribed an oral contraceptive (o.c.), Ortho-Novum 1/80, manufactured by the defendant. This is an "ethical" drug, one obtainable only upon prescription, as distinguished from a "proprietary" or "patent" drug, one sold over the counter. Plaintiff was in good health at that time; her blood pressure was 100/56, and she had never had any problems with her kidneys or with high blood pressure. She took Ortho-Novum 1/80, as prescribed by her physician, continuously from the fall of 1972 until June 1976, with the exception of about thirty days in early 1974 when she had a rash on her hand and a physician suggested that she stop taking the pill until the rash went away. She

saw Dr. Hermes in December 1974; his notes reveal nothing remarkable about her health at that time except that her blood pressure was 130/80. The prescription for Ortho-Novum 1/80 was extended for another year. Mrs. Wooderson next saw the doctor in January 1976. His notes reveal nothing remarkable except that her blood pressure was 120/90. She had a cold, and Tuss-Ornade was prescribed for that. The Ortho-Novum 1/80 prescription was also extended for one year. On May 4, 1976, she called Dr. Hermes; she still had a cold, and he called in a prescription for Tuss-Ornade. On June 25, 1976, she again called him. She reported stomach pains and vomiting. Medication to stop the vomiting was prescribed, as was bed rest. Dr. Hermes advised her to

go to the emergencv room at the hospital if she had no relief by that night. Next, on June 28, 1976, Mrs. Wooderson went to the office. Dr. Hermes was not in, and she was examined by one of his associates, Dr. Howard Wilcox. Her blood pressure was 160/88. She complained of abdominal pain, nausea, dizziness, headaches and weakness. She felt like she was coming down with the flu. Dr. Wilcox took her off of the oral contraceptives and prescribed Equagesic. On the following day, she called Dr. Wilcox. She still had headaches, felt weak, was short of breath, and had a sore throat and cough. He directed her to continue with the Tuss-Ornade and the Equagesic. On June 30, she called the office and talked with Dr. Buck, another

associate. He authorized a refill of the Tuss-Ornade prescription. Two days later, on July 2, she saw Dr. Wilcox in his office. She was still vomiting; she complained of exhaustion upon slight exertion; her legs ached; and she had a sore throat but no fever. Her blood pressure had reached 186/104. Dr. Wilcox ordered some tests and later that same day referred her to Dr. Reid, an internist, who examined her and saw all of the laboratory reports. He directed her to the Lawrence Memorial Hospital, which she entered on July 2. Her blood pressure was 202/102. She was diagnosed as having chronic renal disease. Two days later, on Sunday, July 4, 1976, she was transferred by ambulance to the K. U. Medical Center in Kansas City, Kansas.

Upon her arrival at the medical center, she was described as being in poor condition, and she was initially diagnosed as suffering from "renal failure." Peritoneal dialysis was commenced immediately. A few days later, surgery was performed so that she could be connected to the hemodialysis machine. Her kidneys had utterly failed, and she was completely dependent upon hemodialysis. She was released from the K. U. Medical Center on July 28, 1976. The hospital records upon her discharge contain the following case summary:

> "FINAL DIAGNOSIS: Renal failure secondary to hemolytic uremic syndrome, oral contraceptive induced.
> Hypertension, volume dependent.
> Congestive heart failure secondary to volume overload.
> Anemia secondary to #1.

"OPERATIONS AND PROCEDURES: Peritoneal dialysis. Renal biopsy, open. External leg shunt. Internal fistula placement in the left arm.

"DISPOSITION: The patient is discharged on the following medications - Inderal, 20 mg. p.o. q.i.d.; Atarax, 25 mg. p.o. p.r.n. itching Dalmane, 15 mg. p.o. p.r.n. sleep; Coumadin, 2.5 mg. p.o. daily; Colace, 1 tablet p.o. t.i.d; Alu-Caps, 2 tablets p.o. t.i.d.; Renal Vitamin, 1 p.o. daily. The patient will be returning to the Outpatient Dialysis Clinic for thrice weekly in-center dialysis. The patient and husband will undergo home dialysis training in the late summer or early fall.

"PROGNOSIS: Fair."

After plaintiff was discharged, she had to return to the hospital three times weekly from her home in Lawrence for dialysis treatments. In October 1976, she and her husband travelled to the medical center daily for four weeks and took training for home dialysis. In

November, plaintiff got a home dialysis machine, and thereafter her husband gave her the treatments at home. At first, the dialysis took six hours; later it was reduced to five hours, then to four hours. Mrs. Wooderson continued to have blood pressure problems until both of her kidneys were removed surgically on February 1, 1977. She had eye problems, for which she was hospitalized and treated regularly. On March 22, 1977, she had a kidney transplant from her brother. This was unsuccessful; she rejected the donated kidney. It was removed on April 12, 1977.

On May 3, 1981, following dialysis, the plaintiff had very low blood pressure and stomach cramps. The latter grew pro-

gressively worse. She was taken to the Lawrence Memorial Hospital and then transferred by ambulance to the University of Kansas Medical Center on the following morning. Upon arrival, she was described as having severe abdominal pain and having the classic symptoms of peritonitis. Exploratory abdominal surgery was performed immediately. Roughly one-third of her large intestine, the right colon, was found to be gangrenous, and was removed. Bacteria that normally live inside the intestine were found outside, in the peritoneal cavity, and this was the cause of the peritonitis or generalized infection in the abdomen. The surgeon who performed this operation, Dr. George Emory Pierce, M.D., concluded that the plaintiff's difficulty with the

bowel was due to inadequate blood supply to the intestine. This, in turn, was caused by the low blood pressure following dialysis. Mrs. Wooderson recovered well from this abdominal surgery, and was discharged from the hospital on May 22, 1981.

A second kidney transplant performed in November 1981 has proven successful. Since receiving that kidney, plaintiff has had only one minor rejection, and she has not had to go back on the dialysis machine. At the time of trial, she had gotten along well with the new kidney for some thirteen months. Her blood pressure has not been a problem. She still has blind spots in the right eye, and she is taking Imuran and Prednisone, which are

steroids or immunosuppressant drugs, as well as a renal vitamin and Colace, a stool softener. She will have to take the steroids so long as she retains the donated kidney. Because of the risk involved, she will not have children.

Plaintiff's actual out-of-pocket medical expenses up to the time of trial, plus loss of wages and mileage from her home to and from the hospital, exceeded $215,000. Damages sustained and not covered within the monetary figure include future drug expenses (estimated at $28,800), loss of both kidneys, cataracts in both eyes, increased risk of cancer because of the continued ingestion of steroids, inability to have children, loss of blood flow to part of the large

intestine necessitating major abdominal surgery and removal of part of the intestine, risk of further intestinal surgery, and mental anguish, pain and suffering caused by the extended hospitalization, repeated operations, hemodialysis for five and one-half years, loss of her brother's donated kidney, and some fifty-five blood transfusions. Ortho does not argue that the $2,000,000 awarded as compensatory damages is excessive, or that the amount of the award is not supported by the evidence. Instead, Ortho argues that there is no substantial evidence that the oral contraceptives caused plaintiff's kidney failure; that Ortho had no duty to warn of the risk of hemolytic uremic syndrome (HUS); and that even if it did have the duty to warn, its

failure to warn bore no causal relationship to Dr. Hermes' decision to prescribe Ortho-Novum 1/80 for the plaintiff. Thus, Ortho's position is not that plaintiff did not sustain the injuries and damages claimed, but that Ortho did not cause them to occur and is therefore not responsible. It challenges causation and responsibility, not injury.

SUFFICIENCY OF THE EVIDENCE

The rules under which we review the evidence, when challenged as to sufficiency to support a verdict, are familiar. In Cantrell v. R. D. Werner Co., 226 Kan. 681, 684, 602 P.2d 1326 (1979), we said:

> "It has long been the rule that when a verdict is attacked for insufficiency of the evidence, 'the duty of the appellate court extends only to a search of the record for the purpose of determining whether there is any competent substantial evidence to support the findings. The appellate court will not weigh the evidence or pass upon the credibility of the witnesses. Under these circumstances, the reviewing court must review the evidence in the light most favorable to the party prevailing below.' Craig v. Hamilton, 221 Kan. 311, 313, 559 P.2d 796 (1977)."

See also Hand Realty Co. v. Meyers, 234 Kan. 304, 306, 672 P.2d 583 (1983).

Similarly, in Timsah v. General Motors Corp., 225 Kan. 305, 591 P.2d 154 (1979), the rule is concisely stated in Syllabus ¶ 1:

> "When a verdict is attacked on the ground it is contrary to the evidence, it is not the function of this court on appeal to weigh the

> evidence or pass on the credibility of the witnesses. If the evidence with all reasonable inferences to be drawn therefrom, when considered in a light most favorable to the successful party below, will support the verdict this court should not intervene."

"Substantial evidence" is defined as evidence which possesses both relevance and substance and which furnishes a substantial basis of fact from which the issues can reasonably be resolved. In re Certif. of Need App. by Community Psychiatric Centers, Inc., 234 Kan. 802, 806, 676 P.2d 107 (1984); Haddock v. U.S.D. No. 462, 233 Kan. 66, 661 P.2d 368 (1983); Kelly v. Kansas City, Kansas Community College, 231 Kan. 751, 648 P.2d 225 (1982). Stated in another way, "substantial evidence" is such legal and

relevant evidence as a reasonable person might accept as being sufficient to support a conclusion. Kansas Dept. of Health & Environment v. Banks, 230 Kan. 169, 630 P.2d 1131 (1981). In conformity with these rules, we now consider the evidence in the light most favorable to the successful party.

THE PILL AS CAUSATION

Was there substantial, competent evidence that the oral contraceptive Ortho-Novum 1/80 caused plaintiff's hemolytic uremic syndrome (HUS) and the consequent loss of her kidneys? That is the first issue. Plaintiff, in support of her claim that the drug caused her HUS, presented three specialists, Dr. Dennis

Diederich and Dr. Frank Cuppage, both physicians and members of the teaching staff at the K. U. Medical Center, and Dr. John Gabourel, Ph.D., a professor of pharmacology at the Oregon Health Sciences University, formerly the University of Oregon School of Medicine. Through these witnesses she presented many articles published in medical and scientific journals, both here and abroad.

First, a word about hemolytic uremic syndrome, or HUS. A syndrome is not a disease; it is a set or constellation of symptoms which occur together, and which help the physician recognize the condition and set it apart from less serious conditions or diseases indicated when

only one--or at least less than all--of the symptoms are present. "Hemolytic" means causing hemolysis, the destruction of the red blood cells. "Uremic" means caused by or pertaining to uremia, the presence of urine in the blood and the toxic condition thereby produced. Hemolytic uremic syndrome usually first manifests itself with flu-like symptoms--headache, nausea, fatigue, sometimes fever--and with constantly increasing blood pressure. The onset is rapid. HUS is recognizable through three main symptoms or features. These are: (1) acute kidney failure; (2) thrombocytopenia, a marked decrease in the number of blood platelets, small colorless cells in the blood which assist in the coagulation or clotting of the blood; and (3) hemolytic

anemia, a condition in which the blood is markedly deficient in the number of red blood cells. These three symptoms, kidney failure (resulting in uremia or the presence of urinary constituents in the blood), thrombocytopenia, and hemolytic anemia, can be detected through examination of the blood. The syndrome is also reflected in abnormality in the lining or intima of the small blood vessels in the kidney; this causes hemolysis or destruction of the red blood cells moving across the injured lining. Abnormality of the blood vessels of the kidney may be detected pathologically. HUS is extremely serious. Its course is described as being relentlessly downhill, with irreversible kidney failure the usual result.

Dr. Diederich is a professor of medicine in the department of internal medicine at K. U. Medical Center. He is board-certified in internal medicine and also in nephrology. His practice, and the area in which he teaches, consists of diagnosing various problems with the kidney, trying to determine the cause of the kidney ailment, and treating the condition. He has been in the nephrology section of the department of internal medicine at the K. U. Medical Center since 1969. He was alerted by a telephone call from plaintiff's physician in Lawrence, and was present when she arrived at the medical center on July 4, 1976. She was taken directly to the intensive care unit. There, Dr. Diederich observed that her blood pres-

sure was very high. She showed evidence of circulatory overload. Her heart was beating hard, her pulse was pounding and her veins were distended. Her hands and feet were swollen. The breath sounds reflected moisture in the lungs. She was making very, very small amounts of urine, and a catheter in her bladder demonstrated that there was no flow of new urine being made by her kidneys. The blood vessels in her eyes evidenced increased tension. Peritoneal dialysis was employed to relieve the pressure and correct the blood by filtration. Blood tests disclosed that she had less than half of the expected normal amount of red blood cells in a sample of her blood, and a low white blood cell count--2,500 rather than the 4,000 to 6,000 which

would normally be found. Twelve to fifteen pounds of fluid was removed by peritoneal dialysis. Later in the week, a small specimen was taken surgically from plaintiff's kidney, and this was microscopically examined.

Dr. Diederich was furnished with a history of the patient and of the patient's family. He carefully checked on and ruled out infection or any of the other possible causes for plaintiff's condition. He testified that oral contraceptives cause changes in the blood vessels in the kidney. He expressed the opinion that the oral contraceptive taken by the plaintiff was responsible for the destruction of her kidneys and the generation of her malignant hypertension.

When Carol Wooderson first entered the hospital, Dr. Diederich thought that she was suffering from HUS, brought on by the oral contraceptives which she had been taking. He still thought so when she was released from the hospital on July 28, 1976. Thereafter, he read many additional published articles on the subject in various medical journals, dozens of which were received in evidence in this case. When he testified at the trial, Dr. Diederich still believed that the oral contraceptives taken by Carol Wooderson caused her HUS and the resulting loss of her kidneys, the eye problems, and the loss of a section of her intestine.

The testimony of Dr. Francis Edward

Cuppage, M.D., was presented by videotape deposition. Dr. Cuppage is a pathologist, and his area of special interest is in kidney or renal disease. He has been on the teaching staff at the University of Kansas Medical School since 1967, and he has been a full professor since 1973. He practices medicine, teaches, and does research in acute renal failure. He is a board-certified pathologist, and he has published some fifty-four articles in medical journals, most of them related to the kidney. Some are also related to blood supply. He had no direct contact with the plaintiff and had not seen her before his deposition was taken. He is the pathologist in charge of renal biopsies at the K. U. Medical Center. As such, and at the request of

Dr. Diederich, Dr. Cuppage examined a portion of the plaintiff's kidney on July 8, 1976. This portion had been removed by Dr. Arlo Hermrick, a surgeon, by a procedure known as kidney wedge biopsy. One sample was examined in the usual method by microscope, and the other was examined by electron microscopy. When Dr. Cuppage first microscopically examined this tissue, he had not read plaintiff's clinical history and laboratory findings. He had read these materials when later studies were conducted on plaintiff's kidneys, after their removal in early 1977.

Dr. Cuppage explained the microscope slides prepared from the biopsy of Carol Wooderson's kidneys, and he pointed out

the major areas of damage, both in the blood vessels and in the glomeruli, the filters of the kidney. He explained why the slides rule out most of the things which might cause kidney damage. Then Dr. Cuppage expressed the opinion that the contraceptive pill, Ortho-Novum 1/80, can produce an alteration in the blood vessels. He thought that the most probable cause of plaintiff's HUS and her resulting health problems was blood vessel lesions produced by oral contraceptives. The lesions in the small blood vessels in the kidneys came first; hypertension and damage to the glomeruli followed as a result of the vascular lesions. He stated that he was more firmly convinced at the time he was giving his testimony that his original diagnosis was

correct than he had been when he made it. All of the pathological and clinical information which he received later solidified his opinion.

John Gabourel, Ph.D., a professor of pharmacology from the Oregon Health Sciences University, testified at length. He received his Ph.D. degree in pharmacology at the University of Rochester in 1957. He has conducted research on many subjects and has had national level research support for many years. He teaches medical students and nurses at the university, and also participates in continuing education courses for the practicing physicians of his state. Included in the areas he teaches is systematic pharmacology or organ system

pharmacology, which deals with the specific effect of drugs on different tissues and organs of the body. He has authored some thirty-one major publications, plus a lesser number of short articles. In preparing to testify in this case, he read abstracted portions of the medical records of the plaintiff and many original articles that had been obtained previously by Dr. Diederich. He ran a Med.-Line computer search of his own, discovered and read additional articles, consulted Harrison's Textbook of Medicine, and in general read everything that he could find that had been published relating to HUS and particularly to its occurrence in women who have been taking oral contraceptives. He testified that he had spent almost all of

the three weeks before he testified reading and thinking about HUS, running more computer searches in different areas, and talking to other people in specialized areas, including officials of the Food and Drug Administration. He expressed the opinion that Ortho-Novum 1/80, in some women, causes malignant hypertension, vessel wall damage, HUS, and permanent failure of and loss of the kidneys. It was his professional opinion that Ortho-Novum 1/80 caused Carol Wooderson's HUS and the loss of her kidneys.

Among the reasons why this witness concluded that Ortho-Novum 1/80 caused plaintiff's HUS were: (1) Plaintiff took the oral contraceptives long enough for

development of lesions of the type identified by Dr. Nelson Irey as being caused by oral contraceptives; (2) no other agency with known association to HUS was present; (3) the known effects of estrogen (a component of Ortho-Novum 1/80) are compatible with (a) the alteration in blood vessel structure and (b) the enhancement of platelet adhesion and aggregation; (4) there were twenty-one reported cases of women on oral contraceptives having HUS before plaintiff, and at the time of trial there were thirty-nine patient cases reported wherein oral contraceptives were associated with HUS; (5) in two of the reports, there was a "re-challenge"--women who were on oral contraceptives and showed symptoms of HUS were taken off the oral contraceptives

and apparently recovered, were put back on oral contraceptives and suffered severe recurrence of HUS; (6) the pathological examination and report done in February 1977, after plaintiff's bilateral nephrectomy, was consistent with HUS. Dr. Gabourel ruled out as causative agents all of the other drugs which plaintiff had taken prior to the onset of her HUS. It was his opinion that Ortho-Novum 1/80 caused inflammation and occlusion of the inner wall of the tiny arteries in her kidneys. This was followed by kidney failure and then malignant hypertension. He suggested that her January 1976 blood pressure of 120/90 is highly significant, a 30mm rise over her pre-oral contraceptive measurement. Thus it was his opinion that this catastrophy

could have been avoided if her physicians had been properly warned. Warnings would have alerted her physicians to monitor her blood pressure more closely and to conduct various urine and renal function tests earlier in 1976. Early detection could have prevented the irreversible kidney failure.

The testimony of Dr. Diederich and Dr. Gabourel extends through ten volumes of trial transcript. Dr. Cuppage's deposition is also a lengthy document. Other physicians also testified. The brief summaries above reflect but a very small portion of the plaintiff's evidence in this case. Ortho contends that plaintiff's proof of medical causation is "conjectured" and "based on a diagnosis

of exclusion." Upon reviewing this entire record, however, it appears to us that the proof of medical causation is detailed, logical, and based upon scientific studies, commencing with those of pathologist Nelson Irey. One of the requisites for arriving at a conclusion as to cause is to consider all possible causes. Plaintiff's expert witnesses did this, and each gave in detail the reasons why Ortho-Novum 1/80 was the cause, and why each other possible cause of plaintiff's HUS had to be eliminated in this case. We conclude that there is an abundance of substantial, competent evidence to support the jury's finding that Ortho-Novum 1/80 caused the plaintiff's HUS, her acute kidney failure, and her resulting injuries and damages.

DUTY TO WARN

Ortho contends that it had no duty to add to the prescribing instructions for Ortho-Novum 1/80 statement that there might be an association between the use of that product and HUS, malignant hypertension, or acute renal failure. In support of this contention, it cites Restatement (Second) of Torts § 402A (1965), including the comments thereto, and Lindquist v. Ayerst Laboratories, Inc., 227 Kan. 308, 319, 607 P.2d 1339 (1980). Lindquist was a products liability and medical malpractice case brought against Ayerst Laboratories, Inc., the manufacturer of an anesthetic which had been administered to the decedent, and the two physicians who had

administered the anesthetic. Verdict had been entered for the defendants and plaintiff appealed. In the course of the opinion, we said:

> "[T]he jury was properly instructed regarding the doctrine of strict liability expressed in Restatement (Second) of Torts § 402A (1965). The jury was instructed to find Ayerst liable provided they found the drug was in a defective condition and unreasonably dangerous to persons who might be expected to use it, where that defect caused or contributed to the death of Lindquist. The defective condition is the failure of Ayerst to properly warn and instruct the medical profession with respect to the use and possible consequences of the use of Fluothane." 227 Kan. at 319.

Section 402A of the Restatement, together with the applicable portions of Comment j thereunder, read as follows:

"§402A. Special Liability of Seller of Product for Physical Harm to User or Consumer

"(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if

(a) the seller is engaged in the business of selling such a product, and

(b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold.

"(2) The rule stated in Subsection (1) applies although

(a) the seller has exercised all possible care in the preparation and sale of his product, and

(b) the user or consumer has not bought the product from or entered into any contractual relation with the seller.

> j. Directions or warning. . . . Where, however, the product contains an ingredient to which a substantial number of the population are allergic, and the ingredient is one whose danger is not generally known, or if known is one which the consumer would reasonably not expect to find in the product, the seller is required to give warning against it, if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge, of the presence of the ingredient and the danger. Likewise in the case of poisonous drugs, or those unduly dangerous for other reasons, warning as to use may be required." (Emphasis supplied.)

Defendant seizes upon that portion of the comment reading "if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge . . . ." Ortho contends, in essence, that an ethical (prescription) drug manufacturer is not

bound to provide warnings until the occurrence of side effects is so frequent and the evidence of causation so clear-cut that the drug maker is itself convinced that the drug causes or contributes to such problems. This, we conclude, is not the law. A drug manufacturer's duty to warn is discussed and the rules are stated in numerous cases. A leading case in this field is McEwen v. Ortho Pharmaceutical, 270 Or. 375, 528 P.2d 522 (1974). Plaintiff McEwen brought suit against Ortho and Syntex for their alleged failure to give appropriate warning to the medical profession of dangers which the manufacturers knew or had reason to know were inherent in the use of their products. Plaintiff recovered judgment and defendants appealed.

In affirming the judgment, the court said:

"I. DEFENDANTS' DUTY TO WARN PLAINTIFF'S DOCTORS

1. There is no question here of any defect in the manufacture of defendants' oral contraceptives, nor of their efficacy when taken as prescribed. It is well settled, however, that the manufacturer of ethical drugs bears the additional duty of making timely and adequate warnings to the medical profession of any dangerous side effects produced by its drugs of which it knows, or has reason to know. E.g., Sterling Drug, Inc. v. Cornish, 370 F2d 82 (8th Cir 1966); Parke-Davis & Co. v. Stromsodt, 411 F2d 1390 (8th Cir 1969); Stevens v. Parke, Davis & Co., 9 Cal 3d 51, 107 Cal Rptr 45, 507 P.2d 653 (1973); Love v. Wolf, 226 Cal App 2d 378, 38 Cal Rptr 183 (1964); Krug v. Sterling Drug, Inc., 416 SW2d 143 (Mo Sup Ct 1967); see 2 Restatement (Second) of Torts 300, §388 (1965).

"The duty of the ethical drug manufacturer to warn is limited to those dangers which the manufacturer knows, or has reason to know, are inherent in the use of its drug.

However, the drug manufacturer is treated as an expert in its particular field, and is under a 'continuous duty * * * to keep abreast of scientific developments touching upon the manufacturer's product and to notify the medical profession of any additional side effects discovered from its use.' Schenebeck v. Sterling Drug, Inc., 423 F2d 919, 922 (8th Cir 1970); accord O'Hare v. Merck & Co., 381 F2d 286, 291 (8th Cir 1967). The drug manufacturer's duty to warn is, therefore, commensurate not only with its actual knowledge gained from research and adverse reaction reports but also with its constructive knowledge as measured by scientific literature and other available means of communication.

"Although the duty of the ethical drug manufacturer is to warn the doctor, rather than the patient, the manufacturer is directly liable to the patient for a breach of such duty. See Schenebeck v. Sterling Drug, Inc., supra; Love v. Wolf, supra. The manufacturer's compliance with this duty enables the prescribing physician to balance the risk of possible harm against the benefits to be gained by the patient's use of that drug. Moreover, as observed by the court in Sterling Drug, Inc. v. Cornish, supra 370 F2d at 85:

"'*** [T]he purchaser's doctor is a learned intermediary between the purchaser and the manufacturer. If the doctor is properly warned of the possibility of a side effect in some patients, and is advised of the symptoms normally accompanying the side effect, there is an excellent chance that injury to the patient can be avoided. This is particularly true if the injury takes place slowly ***.'

"Although the ethical drug manufacturer's duty to warn has been discussed most often with reference to the prescribing physician, the above reasoning applies with equal force to the treating physician. It is especially important that the treating doctor receive the manufacturer's warnings where it is impossible to predict in advance whether a particular patient is apt to suffer adverse effects from a drug, since the treating doctor may be more likely to observe the actual symptoms of the drug's untoward consequences. If the prescribing physician is entitled to make an informed choice in deciding whether the patient should begin taking a prescription drug, it follows that a treating physician should have the same information in making his decision as to whether the patient should stop taking that drug.

"The duty of the ethical drug manufacturer to warn extends, then, to all members of thc medical profession who come into contact with the patient in a decision-making capacity. To satisfy this duty, the manufacturer must utilize methods of warning which will be reasonably effective, taking into account both the seriousness of the drug's adverse effects and the difficulties inherent in bringing such information to the attention of a group as large and diverse as the medical profession. See Sterling Drug, Inc. v. Yarrow, 408 F2d 978 (8th Cir 1969). The warning should be sufficient to apprise the general practitioner as well as the 'unusually sophisticated medical man' of the dangerous propensities of the drug. Parke-Davis & Co. v. Stromsodt, 411 F2d 1390, 1400 (8th Cir 1969). In short, 'it is incumbent upon the manufacturer to bring the warning home to the doctor.' Rheingold, Products Liability--The Ethical Drug Manufacturer's Liability, 18 Rutgers U L Rev 947, 993 (1964).

"It has been suggested, however, that the manufacturer of a prescription drug should be under no duty to warn the medical profession that its product is dangerous when used by certain allergic or hypersensitive users. It is unreason-

able, so the argument runs, to impose upon the manufacturer a duty to warn doctors of dangers threatening a statistically insignificant number of users. We find this argument unpersuasive.

"In the field of negligence the duty to warn is limited to those dangerous propensities of the drug of which the manufacturer knows, or has reason to know. If allergic reactions are harder to anticipate, this should be taken into account in evaluating the manufacturer's knowledge. It must be remembered that the negligence liability of the ethical drug manufacturer is restricted to those dangers which <u>are</u> foreseeable.

"Furthermore, to simply conclude that it is unreasonable to impose liability where the known danger threatens only a statistically small percentage of the drug's users is to beg the very question of negligence. The size of the class of endangered persons is one--albeit only one--of the factors to be considered in deciding whether the manufacturer's warnings were, in fact, reasonable.

"The ethical drug manufacturer is, then, subject to a duty to warn the medical profession of untoward effects which the manufacturer

> knows, or has reason to know, are inherent in the use of its drug. Sterling Drug, Inc. v. Cornish, supra 370 F2d 82; Parke-Davis & Co. v. Stromsodt, supra 411 F2d 1390; Basko v. Sterling Drug, Inc., 416 F2d 417 (2d Cir 1969); Love v. Wolf, supra 226 Cal App 2d 378; Krug v. Sterling Drug, Inc., supra 416 SW2d 143; cf. Davis v. Wyeth Laboratories, Inc., 399 F2d 121 (9th Cir 1968). See also Wright v. Carter Products, Inc., 244 F2d 53 (2d Cir 1957); Hungerholt v. Land O'Lakes Creameries, Inc., 209 F Supp 177 (D Minn 1962), aff'd 319 F2d 352 (8th Cir 1963); Gerkin v. Brown & Sehler Co., 177 Mich 45, 143 NW 48 (1913). But see Winthrop Laboratories Division of Sterling Drug, Inc. v. Crocker, 502 SW 2d 850 (Tex Civ App 1973)." 270 Or. at 385-390.

In determining whether there was a breach of defendant's duty, the Oregon court said:

> "Because the ethical drug manufacturer has only the duty to warn the medical profession of those adverse effects of which it knows, or has reason to know. the adequacy of the warnings given by each defendant

> depends upon the actual and constructive knowledge of that defendant before and during the period in which Mrs. McEwen used its drug. For Syntex, the relevant interval began on December 3, 1966, when plaintiff first took Norinyl, and ended on December 20, 1967, when she changed to Ortho-Novum oral contraceptives. From that date, plaintiff used Ortho-Novum until approximately December 22, 1968, and this is the relevant time span with reference to Ortho's knowledge.
>
> . . . .
>
> "Numerous studies, reports and other documents were admitted into evidence and discussed by the expert witnesses. Some of these materials support Mrs. McEwen's contention that defendants knew, or should have known, of the dangerous propensities of their oral contraceptives during the time plaintiff was using them." 270 Or. at 390-91.

Thereafter, the court discussed testimony of experts, a cooperative two-year oral drug safety study conducted by Ortho and Syntex, a 1965 article pub-

lished in Archives of Ophthalmology, and various package inserts. The court then stated:

> "Viewing all the testimonial and documentary evidence in its entirety, there was substantial evidence that each defendant knew, or should have known, that its oral contraceptive had a dangerous propensity to cause the kind of harm suffered by plaintiff. This is not to say that defendants did not produce substantial evidence tending to prove that they did not have such knowledge during the relevant times. Our sole function, however, has been completed by our determination that reasonable men might differ upon the point. It was for the trier of fact to resolve the conflict." 270 Or. at 395-96.

In Ortho Pharmaceutical v. Chapman, 180 Ind.App. 33, 388 N.E.2d 541 (1979), the Court of Appeals of Indiana, Fourth District, said:

"We are persuaded that the duty to warn under Comment k does not arise until the manufacturer knows or should know of the risk. [Citations omitted.] In the case of drug manufacturers, the standard of constructive knowledge is that of an expert in that particular field. Reyes v. Wyeth Laboratories, Inc. (5th Cir. 1974), 498 F.2d 1264 [citations omitted]. . . . [D]ates are 'vitally important' with respect to the duty to warn. Because a manufacturer cannot be required to warn of a risk unknown to science, the knowledge chargeable to him must be limited to that of the period during which the plaintiff was using the product in question. [Citations omitted.]

"A second important limitation on liability . . . applies to manufacturers of ethical [prescription] drugs. Since such drugs are available only by prescription, a manufacturer's duty to warn extends only to the medical profession, and not the ultimate users. [Citations omitted.] Terhune v. A. H. Robins Co. (1978), 90 Wash.2d 9, 577 P.2d 975. The rationale for this exception to the Restatement's general rule is that 'Prescription drugs are likely to be complex medicines, esoteric in formula and varied in effect. As a medical expert, the prescribing physician can take into

account the propensities of the drug, as well as the susceptibilities of his patient. His is the task of weighing the benefits of any medication against its potential dangers. The choice he makes is an informed one, an individualized medical judgment bottomed on a knowledge of both patient and palliative.'

Reyes v. Wyeth Laboratories, Inc., supra. The court in Terhune v. A. H. Robins Co., supra, elaborates further:

'The reasons for this rule should be obvious. Where a product is available only on prescription or through the services of a physician, the physician acts as a 'learned intermediary' between the manufacturer or seller and the patient. It is his duty to inform himself of the qualities and characteristics of those products which he prescribes for or administers to or uses on his patients, and to exercise an independent judgment, taking into account his knowledge of the patient as well as the product. The patient is expected to and, it can be presumed, does place primary reliance upon that judgment. The physician decides what facts should be told to the patient. Thus, if the product is properly labeled and carries the necessary instructions and warnings

to fully apprise the physician of the proper procedures for use and the dangers involved, the manufacturer may reasonably assume that the physician will exercise the informed judgment thereby gained in conjunction with his own independent learning, in the best interest of the patient. It has also been suggested that the rule is made necessary by the fact that it is ordinarily difficult for the manufacturer to communicate directly with the consumer. (Footnote omitted.)'

"In summary, a proper warning under Comment k in the context of the facts at bar, communicates a risk attendant on the use of the product which is known to experts in the field during the period in which the product is used. It need only be directed to doctors, not patients who are the ultimate users.

. . . . .

"To summarize, a product which is faultlessly designed and manufactured may be nevertheless unreasonably dangerous within the meaning of §402A if not accompanied by proper warnings. A manufacturer can only be required to warn of risks known during the time in which the plaintiff was using the product in question, however he is charged with the knowledge of an expert in that

field. In the case of ethical drugs, the manufacturer's duty is discharged if adequate warning is given to doctors, who act as 'learned intermediaries' between the manufacturer and the ultimate user. To be adequate, a warning must be reasonable under the circumstances. As a practical matter, this is determined by application of negligence theory.

"As proof of the inadequacy of Ortho's warnings, Chapman offered into evidence the full text of the written warnings in question and expert testimony as to the state of knowledge in the medical profession at the time. Ortho argues that the plaintiff's expert was not qualified to give an expert opinion as to the adequacy of the warnings since he had no special training or experience in reading and writing warnings. This is not the test:

"'The true rule appears to be fairly stated in the case of Isenhour v. State, 1901, 157 Ind. 517, 528, 62 N.E. 40, 44, 87 Am.St.Rep. 228, in which this court said: "Courts have never undertaken to set up a standard of scientific knowledge by which the competency of a witness may be determined, and have not gone to the extent of holding that a scientific witness can only testify from facts learned by

him from personal demonstration. The general rule in such cases, in this state, at least, seems to be that, where a witness exhibits such a degree of knowledge, gained from experiments, observation, standard books, or other reliable source, as to make it appear that his opinion is of some value, he is entitled to testify leaving to the trial court, in the exercise of a sound discretion, the right to say when such knowledge is shown, and to the jury the right to say what the opinion is worth; and, as in all other cases of discretion, this court will review the action of the trial court only when that discretion clearly appears to have been abused."'

Illinois Steel Co. v. Fuller (1939), 216 Ind. 180, 23 N.E.2d 259, 263. Our review of this expert's qualifications convinces us that clearly there was no abuse of discretion in permitting his testimony. Regarding the state of knowledge in the medical profession at the time, the expert testified that 'statistics were being published to show the direct relationship of the oral contraceptive pill to an increased disposition in women to develop blood clotting. . . .' The expert then summarized several reports of studies. He was asked, 'Was there information in the year 1968 available to the defendant here from

these studies, you take the Wright Committee, the British Studies, the Hellman Reports, that did establish a relationship between the use of the pill and thrombophlebitis?' The expert responded 'yes.' The expert was then requested to read aloud the following portion of Ortho's 1968 Physicians Desk Reference entry for Ortho-Novum: 'No comparable studies are yet available in the United States. The British data, <u>especially as they indicate the magnitude of the increased risks</u> to the individual patient, <u>cannot be directly applied to women in other countries</u> in which the incidences of spontaneously occurring thromboembolic disease may be different.' (Emphasis added). The expert was asked to state his opinion of the adequacy of the warning. After objections, preliminary questions, a recess, and more objections, he stated that in his opinion the warnings were 'insufficient, incomplete and misleading.'" 180 Ind.App. at 42-44, 50-52.

Again, with reference to the manufacturer's duty to warn the Second Circuit in <u>Lindsay v. Ortho Pharmaceutical</u>

Corp., 637 F. 2d 87 (2d Cir. 1980), said:

> "The manufacturer's duty is to warn of all potential dangers which it knew, or in the exercise of reasonable care should have known, to exist. Baker v. St. Agnes Hospital, supra, 70 App.Div.2d at 405, 421 N.Y.S.2d 81; Tinnerholm v. Parke-Davis & Co., 285 F.Supp. 432, 451 (S.D.N.Y. 1968), aff'd on other grounds, 411 F.2d 48 (2d Cir. 1969). The duty is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge of its products as gained through research, adverse reaction reports, scientific literature, and other available methods. Baker v. St. Agnes Hospital, supra, 70 App.Div.2d at 406, 421 N.Y.S.2d 81. Except where FDA regulations otherwise provide, the manufacturer's duty is to warn the doctor, not the patient. The doctor acts as an 'informed intermediary' between the manufacturer and the patient, evaluating the patient's needs, assessing the risks and benefits of available drugs, prescribing one, and supervising its use. Wolfgruber v. Upjohn Co., supra, 72 App.Div.2d at 61, 423 N.Y.S.2d 95." 637 F.2d at 91.

Brochu v. Ortho Pharmaceutical Corp., 642 F.2d 652 (1st Cir. 1981), is another case in which the adequacy of warnings was involved. That court said:

> "An adequate warning is one reasonable under the circumstances. Sterling Drug, Inc v. Yarrow, 408 F.2d 978, 992, 993 (9th Cir. 1969); Ortho Pharmaceutical Corp. v. Chapman, 388 N.E.2d at 553. A warning may be inadequate in factual content, in expression of the facts, or in the method by which it is conveyed. Ortho Pharmaceutical Corp. v. Chapman, 388 N.E.2d at 552.
>
> "The adequacy of the warning must be judged in the light of what Ortho knew at the time Mrs. Brochu was actually taking Ortho-Novum 2 mg. The key document in this determination is a study conducted by Inman, Vessey, Westerholm, and Engelund and published in the British Medical Journal in April 1970. Their research found a 'positive correlation . . . between the dose of oestrogen [estrogen] and the risk of . . . cerebral thrombosis.' It also noted that estrogen dosage might not be the only factor related to the risk of thrombo-

embolism. Ortho has not claimed that it was unaware of this study, but the report was not cited in the package insert for the 2 mg. oral contraceptive or in the package insert for any other Ortho oral contraceptive; in fact, the insert for each of these products was identical.

. . . .

"The absence of any reference to the 1970 British study, which, unlike the four studies actually referred to in the package insert, would have provided numerical data to the physician on the dose-effect relationship between thromboembolic disease and oral contraceptives, was ground for a jury finding that the warnings were factually inadequate. To this is to be added the fact that the inserts for each of Ortho's oral contraceptives were identical, despite this evidence that higher-estrogen-dose pills might present greater risks to users. From this, the jury mght have concluded that the warnings for the 2 mg. pills were inadequate. The jury might also have considered on the question of warning the fact that the sales-person who regularly called on Dr. Campbell did not orally inform him that the 2 mg. drug appeared to present a higher risk of thrombo-embolism. See Sterling Drug, Inc.

v. Yarrow, 408 F.2d at 992, 993 (trial court may find it unreasonable to fail to instruct sales personnel to warn physicians on whom they call regularly of drug dangers; not clearly erroneous to find such sales personnel present most effective method of warning doctors).

"In view of the expert testimony that the April 1970 study did establish the existence of a positive correlation between the dose of estrogen and the risk of cerebral thrombosis, and the admitted fact that the labeling did not refer to this study, Ortho's claim that the Brochus did not provide expert testimony on the inadequacy of the label is untenable." 642 F.2d at 657-59.

One other case is illuminating. In Seley v. G. D. Searle & Co., 67 Ohio St. 2d 192, 423 N.E.2d 831 (1981), the Supreme Court of Ohio discussed the adequacy of warnings. It said:

"A jury may find that a warning is inadequate and unreasonable even

> where the existence of a 'risk,' i.e., a causal relationship between use of the product and resulting injury, has not been definitely established. McCue v. Norwich Pharmacal Co. (C.A. 1, 1972), 453 F.2d 1033; Hamilton v. Hardy, [37 Colo.App. 375, 549 P.2d 1099 (1976)]. Thus, where scientific or medical evidence exists tending to show that a certain danger is associated with use of the drug, the manufacturer may not ignore or discount that information in drafting its warning solely because it finds it to be unconvincing. Mahr v. G. D. Searle & Co. [72 Ill.App.3d 540, 390 N.E.2d 1214 (1979)], at page 564." (Emphasis supplied.) 67 Ohio St. 2d at 198

An enlightening discussion of recent cases involving the duty of an ethical drug manufacturer to warn is found in Scott, Products Liability, 1982 N.Y.U. Ann. Surv. Am. L. 709, 720-24:

"DUTY TO WARN OF THE DANGERS
INHERENT IN DRUGS

"Drug manufacturers have a duty to warn medi-cal practitioners about products which, though useful, are unavoidably unsafe. An unusual result was reached in Lukaszewicz v. Ortho Pharmaceutical Corp. [510 F.Supp. 961 (E.D. Wis. 1981)], where the District Court for the Eastern District of Wisconsin held that the manufacturer of an oral contraceptive had the duty to warn not only the doctor, but also the patient, of the potential risks involved in taking the drug. The court imposed this duty to warn even though the drug was available only by prescription.

"In Lukaszewicz, the plaintiff alleged that use of the contraceptive caused her to suffer severe migraine headaches which ultimately resulted in a cerebrovascular injury. She claimed that Ortho had a duty to warn patients directly of the possible side effects of the drug.

"The court based its decision on an FDA regu-lation which, when read together with Wisconsin law, spelled out a case for negligence per se. The FDA regulation sets out detailed instructions regarding the required warnings to be directed to

users of oral contraceptives in a package insert. While other federal courts have been aware of FDA regulations about drug labeling, the court noted that none has held that a drug manufacturer's duty extends beyond warning the doctor. The law in Wisconsin, however, provides that violation of state and federal legislative and administrative enactments designed to protect a particular class of persons, which results in the proscribed harm, constitutes negligence per se. The court, therefore, held that the defendant drug company breached its duty to the plaintiff, because the purpose behind the FDA regulation was to enable patients taking oral contraceptives to recognize harmful side effects and seek medical assistance, and because violation of the regulation by the manufacturer allegedly led to the harm which thc plaintiff suffered. The plaintiff's claim that she received no warning, as well as the issue of causation, became questions of fact for jury resolution.

"In light of the explicit requirements set out by the FDA regarding oral contraceptive labeling, the court's decision is clearly correct. Since there is no reason to promulgate regulations if they will not be enforced, one can only wonder why other courts have not

arrived at the conclusion reached in Lukaszewicz.

"In another case involving oral contraceptives, Brochu v. Ortho Pharmaceutical Corp. [642 F.2d 652 (1st Cir. 1981)], the Court of Appeals for the First Circuit, interpreting New Hampshire law, applied the strict liability standard to a prescription drug. The plaintiff's doctor had prescribed the defendant's two-milligram, high estrogen content oral contraceptive which the plaintiff took for over three years until, allegedly as a result of taking the drug, she suffered a stroke. The First Circuit upheld the plaintiff's claim that Ortho should have warned doctors that the estrogen content pill posed a high risk of cerebral damage and that failure to so warn rendered Ortho liable for manu-facturing a defective and unreasonably dangerous product.

"The court noted that certain drugs, though very useful, often cannot be made absolutely safe. Where such is the case, a manufacturer can avoid liability if it adequately warns of the dangers presented by the drug. An adequate warning is to be judged in light of what the manufacturer knew at the time the plaintiff took the drug. The court placed heavy emphasis on a

British study that established a positive correlation between a drug's estrogen content and the risk of stroke. The study had been published over a year before the plaintiff suffered her accident and yet Ortho did not mention the study in either the written or oral information it supplied to prescribing physicians. Additionally, in finding the warning accompanying the two-milligram contraceptive inadequate, the court noted that Ortho's labeling for all its oral contraceptives was identi-cal, despite evidence that the higher estrogen pills posed greater risks.

"The court next addressed the issue of causation and found that the defendant's failure to warn was the proximate cause of the plaintiff's injury. The plaintiff's doctor testified that if he had been alerted to the increased risk of the two-milligram pill he would not have prescribed it. The court held that, even if the doctor was careless in not prescribing the equally effective lower dosage pill, Ortho would not be relieved from liability because its failure to warn may have contributed to the doctor's carelessness.

"In contrast, the decision by the Court of Appeals for the Fourth Circuit in Stanback v. Parke-Davis

& Co. [657 F.2d 642 (4th Cir. 1981)] insulated a drug manufacturer from liability for failure to warn of the risks associated with its flu vaccine; the court affirmed the summary judg-ment granted to the defendant. The plaintiff in this case contracted Guillain-Barre Syndrome after being innoculated with the defendant's vaccine. She argued that the manufacturer's failure to pro-vide physicians with information about the risk of Guillain-Barre Syndrome constituted a breach of duty to warn of the potential dangers of the vaccine.

"The court, however, held that since the plaintiff was not able to show that the failure to warn was the cause of her injury, she could not recover from the manufacturer. Whether or not Parke-Davis breached its duty was considered irrelevant because there was clear evidence that the plaintiff's doctor was aware of the risk inherent in the vaccine but administered it anyway. The doctor also stated that he did not customarily pass on manufacturers' warnings to his patients. Therefore, reasoned the court, the doctor was an intervening cause, relieving the manufacturer of liability for its failure to warn.

"The three aforementioned cases can be reconciled by assessing what

each court thought may have been the potential effect of an adequate warning. In Lukaszewicz, a direct warning to the patient by means of a package insert may have alerted the plaintiff to the cause of her migraines and prompted her to seek medical attention in time to prevent any serious problem. Similarly, in Brochu, a warning to the patient's physician regarding the potential side effects of the two-milligram pill may have prompted him to prescribe a lower dosage, thus substantially reducing the patient's risk of injury. In Stanback, however, any warning the manu-facturer might have given apparently would have had no effect in light of the doctor's firm testimony that he would have administered the vaccine anyway. Here the manufacturer's breach of duty was not a cause of the plaintiff's injury. The Stanback court noted that had the testimony of the doctor indicated that he might have heeded a warning, a different result would have been reached. That result would have been identical to that reached in Brochu."

During the times relevant to this lawsuit, the label which accompanied

Ortho-Novum 1/80, when purchased by the patient, instructed the patient not to take the drugs without her doctor's continued supervision. It warned that the drug could cause side effects, but it did not elaborate upon those side effects except to say that the most serious known side effect was abnormal blood clotting. The "package insert" which is sent to the physician and which contains the information included in the Physicians' Desk Reference (PDR), an annual volume provided for use by physicians, presented detailed instructions, contraindications, warnings, and precautions. It is undisputed, however, that none of these warned of any possible association between the use of the product and HUS, malignant hypertension, or acute renal

failure. Dr. Hermes, plaintiff's gynecologist' testified in substance that he probably would have lowered the dosage had he been informed by Ortho of these potential dangers. Ortho had access to literature that should have prompted it to inform Dr. Hermes of what he needed to know. The expert testimony and the exhibits in this case disclose that there was an abundance of published information in the medical journals, prior to and during the years when plaintiff was taking Ortho-Novum 1/80, which linked the use of oral contraccptives with HUS, malignant hypertension, and acute renal failure. We agree with the McEwen and Seley courts. The available scientific literature clearly tended to show that there was danger of HUS, malignant hyper-

tension and acute kidney failure attendant to the use of the drug. Ortho, as an expert in the field, knew or should have known of the risk. We conclude that, on the basis of the evidence, Ortho had a duty to warn the prescribing physician, and the trial court properly submitted to the jury the issue of the adequacy of Ortho's published warning.

We hold that the manufacturer of an ethical drug has a duty to warn the medical profession of dangerous side effects of its products of which it knows, has reason to know, or should know, based upon its position as an expert in the field, upon its research, upon cases reported to it, and upon scientific development, research, and publications

in the field. This duty is continuing. We do not need to determine, in this case, what duty, if any, such a manufacturer has to warn the ultimate consumer, the patient. Here, neither was warned by Ortho, but Ortho's failure to warn the physician is sufficient to sustain the finding of negligence or breach of duty against it in this case.

Ortho also argues that the FDA has determined that contraceptive-induced HUS does not merit warnings, and that the courts of Kansas must defer to the FDA's determination. This argument centers around a letter from the FDA to Searle Laboratories. Searle had proposed fifteen or more package insert changes, covering many and varied subjects. Only

one of those mentioned the inclusion of HUS as a possible side effect. The FDA responded that it did not concur with the additional changes included in that proposal. This letter cannot be construed as a clear determination by the FDA that contraceptive-induced HUS does not merit warnings, and thus this argument has no merit.

FAILURE TO WARN AS CAUSATION

Ortho next contends that its failure to warn of the association between the use of its product and HUS, malignant hypertension, and acute renal failure was not a cause in fact of plaintiff's injury. To the contrary, we think the evidence was substantial that it was.

There was abundant evidence that the early diagnosis of HUS, of malignant hypertension, and of kidney failure is extremely important. In addition, Dr. Hermes testified that he has two of his daughters on a lower dosage of Ortho-Novum 1/50 because of what he has learned as a result of this case. There was evidence indicating that a lower dosage might have prevented HUS, and even if the higher dosage of estrogen contained in Ortho-Novum 1/80 were given, Mrs. Wooderson's attending physicians--if warned of the possibility of HUS--might have made an earlier diagnosis which, according to the expert testimony, might have averted the tragedy. Dr. Hermes testified that he is now alerted to the danger and would look for symptoms. The

duty to warn, of course, extends throughout the time that the plaintiff was taking Ortho-Novum 1/80. No warnings were given by Ortho during that period of time, and thus the physicians were not informed to be on the alert for symptoms of HUS, kidney failure, or malignant hypertension. The question of whether this failure to warn was a cause of plaintiff's injury was properly submitted to the jury. With respect to warnings, the Chapman court said:

> ". . . Comment j provides a presumption that an adequate warning would be heeded. This operates to the benefits of a manufacturer where adequate warnings in fact are given. Where warnings are inadequate, however, the presumption is in essence a presumption of causation." 180 Ind.App. at 55.

Similarly, the Seley court said:

> "'What the doctor might or might not have done had he been adequately warned is not an element plaintiff must prove as a part of her case.' Hamilton v. Hardy [37 Colo.App. 375, 549 P.2d 1099 (1976)], at page 387. The evidence provided by Dr. Froelich as to his independently acquired knowledge is insufficient to rebut the presumption established by Comment j." 67 Ohio St. 2d at 201-202.

In this case, the warning was inadequate. On the evidence before it, the jury was entitled to find that this inadequate warning caused Mrs. Wooderson's injuries.

Ortho also contends that plaintiff's other theories--failure to test and a "design defect" claim--are not supported by the evidence. The case was submitted

to the jury on the theory of failure to warn. Failure to test was mentioned in the instructions, but was not made a specific basis for recovery of compensatory damages. We will discuss it later in connection with the punitive damages issue. We note, however, that there was evidence on which the jury could have found that Ortho had not fully tested its product in that it had not examined certain renal blood vessels during its animal studies, after renal blood vessel lesions attributable to oral contraceptives had been reported. The design defect claim is based upon the fact that the dangers of HUS, malignant hypertension and acute kidney failure are considerably reduced when a lower dosage is administered, such as that contained

in Ortho-Novum 1/50. There was some evidence in the case to support this claim; however, the matter was not submitted to the jury and was not made a basis for recovery of compensatory damages. We find no error.

COMPARATIVE NEGLIGENCE

Ortho next argues that the trial court erred in refusing to submit the issue of comparative fault of the plaintiff and of the plaintiff's physicians, Dr. Hermes and Dr. Wilcox, to the jury. This argument is made in light of K.S.A. 60-258a, which reads in part as follows:

> "60-258a. Contributory negligence as bar to recovery in civil actions abolished, when; award of damages based on comparative negli-

gence; imputation of negligence, when; special verdicts and findings; joinder of parties; proportioned liability. (a) The contributory negligence of any party in a civil action shall not bar such party or said party's legal representative from recovering damages for negligence resulting in death, personal injury or property damage, if such party's negligence was less than the causal negligence of the party or parties against whom claim for recovery is made, but the award of damages to any party in such action shall be diminished in proportion to the amount of negligence attributed to such party. If any such party is claiming damages for a decedent's wrongful death, the negligence of the decedent, if any, shall be imputed to such party.

"(b) Where the comparative negligence of the parties in any such action is an issue, the jury shall return special verdicts, or in the absence of a jury, the court shall make special findings, determining the percentage of negligence attributable to each of the parties, and determining the total amount of damages sustained by each of the claimants, and the entry of judgment shall be made by the court. No general verdict shall be returned by the jury.

. . . .

> "(d) Where the comparative negligence of the parties in any action is an issue and recovery is allowed against more than one party, each such party shall be liable for that portion of the total dollar amount awarded as damages to any claimant in the proportion that the amount of his or her causal negligence bears to the amount of the causal negligence attributed to all parties against whom such recovery is allowed."

We have held that the intent and purpose of the legislature in adopting the statute is to impose individual liability for damages based on the proportionate fault of all of the parties to an occurrence which gave rise to the injuries and damages, whether or not those persons are joined formally as parties to the action. Brown v. Keill, 224 Kan. 195, 580 P.2d 867 (1978). We have also held that a defendant who seeks

to reduce his percentage of fault by comparing the fault of another party has the burden of proving the other party's fault by a preponderance of the evidence. McGraw v. Sanders Co. Plumbing & Heating, Inc., 233 Kan. 766, 667 P.2d 289 (1983). This follows the general rule that the burden of proof is upon the party asserting the affirmative of an issue. See Jensen v. Jensen, 205 Kan. 465, 467, 470 P.2d 829 (1970); Wycoff v. Board of County Commissioners, 191 Kan. 658, 665, 383 P.2d 520 (1963); 31A C.J.S., Evidence § 104; 29 Am. Jur. 2d, Evidence § 130.

Ortho, in its answer, alleged that if the plaintiff sustained injury, she was guilty of negligence which contri-

buted directly and proximately as a cause of her injuries, and that she failed to use the product in the manner intended. The answer also alleged that plaintiff's injuries, if any, were caused by the negligence of other parties for whom Ortho is not responsible. Dr. Hermes and Dr. Wilcox, who were plaintiff's gynecologists, were originally joined by the plaintiff as defendants in this action. They remained in the action at the time of the pretrial conference. At that time, the plaintiff enumerated various claims against Ortho, and she enumerated her claims of negligence as to Dr. Hermes and Dr. Wilcox. Ortho's position was fully set out in the resulting pretrial order, which included Ortho's claim that:

> "Plaintiff's injuries, if any, were caused by plaintiff's own causal negligence, or by the causal negligence of other defendants for whom this defendant is not responsible, and said negligence either individually or combined was equal to or greater than any causal negligence of this defendant . . . ."

Also included in the pretrial order was a specific designation of all of the witnesses, expert and lay, which each of the parties intended to call during the trial of this action, and all of the exhibits each intended to offer. During the pretrial conference, Ortho's position regarding the actions of Doctors Hermes and Wilcox was clarified as shown by the following excerpt of the transcript of that hearing:

> "MR. MICHAUD: Do you contend, Mr. Wall, any departure from stand-

ard approved medical practice on the part of the defendant doctors?

"MR. WALL: No.

"MR. MICHAUD: So, so far as you are concerned, they did nothing wrong in the use of Ortho-Novum in the plaintiff?

"MR. WALL: No.

. . . .

"MR. MICHAUD: All right, you are not contending in this case that the doctors did anything wrong?

"MR. WALL: No, Gerry.

. . . .

"MR. MICHAUD: Your Honor, I would ask the Court to require Mr. Wall to state whether or not it is one of their defenses in this case that the doctors did anything wrong insofar as causing plaintiff's injury.

. . . .

"MR. WALL: Gerry, I don't plan to bring any experts on that subject and have no reports. Now, if I was going to bring that kind of evidence, I would agree you are entitled to it.

"Now, I don't agree, though, however, that, if at the completion of Gerry's lawsuit, all of the evidence points to the doctor and is marginal as to me, that I am precluded from saying under the evidence that it would appear to me that the evidence against the defendant Ortho-Novum is slight or minimal, at least, and it appears that Mr. Michaud has produced a great case against the doctors, and I think based on the evidence you will find for the defendant Ortho-Novum. I am not precluded from that. I don't think Bud [Mr. H. W. Fanning, who then represented Dr. Hermes and Dr. Wilcox] can be precluded at the completion of saying the same thing.

"THE COURT: I understand what you are saying is you don't intend to offer any evidence that the doctors did anything wrong.

"MR. WALL: That's exactly right."

After the pretrial conference, and shortly prior to trial, plaintiff settled with Dr. Hermes and Dr. Wilcox, with the

result that there remained no claims against the two treating physicians at the time of trial. After settlement, both doctors made motions for summary judgment which were sustained by the trial court. We do not deem it important to this discussion to deal with the mechanics by which the physicians were removed from the case; a simple dismissal of plaintiff's claims, with prejudice, would have accomplished the same result. Ortho objected to the dismissal of the physicians, and at trial sought to have their negligence compared. The trial court said:

> "My conclusion is simply that as far as what's happened, the machinery was there and any time Ortho wanted to put the negligence of the doctors in issue as between Ortho and the doctors, they could

> have done that. . . . Mr. Michaud's questions at the Pretrial Conference were nothing less than an invitation to do that. The invitation was declined. . . . All negligence of the doctors has been removed by Mr. Michaud from this action. It's not in issue. It will not be compared. We are directly at issue with the questions raised by the plaintiff against the defendant Ortho."

As discussed at length earlier in this opinion, plaintiff's principal claim against Ortho was that it failed to give an adequate warning to her physicians of the possibility that Ortho-Novum 1/80 could cause HUS, malignant hypertension or acute renal failure. It was undisputed that no such warning was specifically given in the literature provided by Ortho to the physicians. Ortho was hardly in a position to come forth with a vigorous assertion that the physicians

were negligent in their treatment of the plaintiff since Ortho had not warned the physicians of the risks and had not alerted them. Plaintiff's counsel, at pretrial, was concerned with Ortho's position, as reflected in the discussion quoted above. If no settlement was effected, plaintiff needed to be prepared to meet any evidence produced by Ortho of the negligence of the treating physicians. Ortho's position was clearly stated: It made no claim that the physicians departed from approved medical practice, and if intended to offer no evidence that the physicians did anything wrong. If the plaintiff's evidence were to disclose fault on the part of the physicians, Ortho reserved the right to argue that. When the matter

went to trial, plaintiff offered no evidence of causal negligence on the part of the physicians, and thus it was not necessary for the trial court to submit that issue to the jury. There was no evidence, expert or otherwise, of actionable, causal negligence on the part of Drs. Hermes and Wilcox. Under the circumtances disclosed by the record and the evidence in this case, we conclude that the trial court did not err in refusing to submit the issue of the comparative negligence of the physicians to the jury.

As to the claimed negligence on the part of the plaintiff, Ortho points only to the evidence that plaintiff did not go to the hospital emergency room on June 25 after she was told by her physician to do

so if she did not get better by 6:00 o'clock that evening. Whether she felt better by evening, we do not know. There is no testimony, medical or otherwise, which suggests that this failure to go to the hospital on June 25 caused or contributed to her injuries or that her condition was reversible on June 25. She saw Dr. Wilcox on June 28, and he did not send her to the hospital at that time. There is, however, testimony that diagnosis and treatment several months earlier might have averted the disaster. We find no evidence to support the submission of Mrs. Wooderson's causal negligence to the jury.

THE PUNITIVE DAMAGE CLAIM

Ortho next claims that the punitive

damage claim should not have been submitted to the jury. It contends that the failure to warn of all potential dangers which an inherently dangerous product such as a prescription drug might cause cannot support a punitive damage award. It contends that there was no evidence of a willful or wanton failure to warn of a known or established defect or danger. It contends that in 1976 there was at most a suggestion that oral contraceptives caused HUS and that the existence of this "suggestion" has neither been confirmed nor refuted; therefore, without proof that there is in fact an increased risk, there is no proof that Ortho willfully failed to warn of the risk. Plaintiff contends that punitive damages were proper because Ortho failed to warn of

HUS, malignant hypertension, vessel wall damage and acute kidney failure after it knew or should have known of the risks, and--in effect--that Ortho put its own financial interests ahead of its duty to the patients taking its pharmaceuticals. We note that it was not until January, 1977, after plaintiff's kidneys failed, that Ortho first included in its package insert a warning under "adverse reactions reported in users of oral contraceptives," an association neither confirmed nor refuted, of "impaired renal function." Even that and later package inserts do not warn of acute renal failure, malignant hypertension, or HUS.

It will be helpful here to review briefly some of the applicable rules

governing punitive damages. In Cantrell v. R. D. Werner Co., 226 Kan. 681, 602 P.2d 1326 (1979), we said:

> "The Court of Appeals has recently given an expansive discussion of the rules relating to punitive damages in the case of Sanders v. Park Towne, Ltd., 2 Kan.App.2d 313, 318-19, 578 P.2d 1131, rev. denied 225 Kan. 845 (1978):
>
> '[P]unitive damages "are permitted whenever the elements of fraud, malice, gross negligence, or oppression mingle in the controversy. (Malone v. Murphy, 2 Kan. 250; Albert Wiley v. Keokuk, 6 Kan. 94; and Cady v. Case, 45 Kan. 733, 26 Pac. 448.) Such damages are allowed not because of any special merit in the injured party's case, but are imposed by way of punishing the wrongdoer for malicious, vindictive or a willful and wanton invasion of the injured party's rights, the purpose being to restrain and deter others from the commission of like wrongs. (Stalker v. Drake, 91 Kan. 142, 136 Pac. 912; see, also, Townsend v. Seefeld, 102 Kan. 302, 169 Pac. 1157; 15 Am. Jur., Damages, § 266, p. 700.)" Watkins v. Layton,

182 Kan. 702, 705, 324 P.2d 130 (1956).' See also Newton v. Hornblower, Inc., 224 Kan. 506, 582 P.2d 1136 (1978); Koch v. Merchants Mutual Bonding Co., 211 Kan. 397, 402, 507 P.2d 189 (1973).

"In Henderson v. Hassur, 225 Kan. 678, 594 P.2d 650 (1979), this court stated:

'The law establishes no fixed ratio between actual and exemplary damages by which to determine excessiveness. In assessing punitive damages the nature, extent, and enormity of the wrong, the intent of the party committing it, and all circumstances attending the transaction involved should be considered. Any mitigating circumstances which may bear upon any of the above factors may be considered to reduce such damages. Will v. Hughes, 172 Kan. 45, 55, 238 P.2d 478 (1951). In fixing an award of punitive damages a jury may consider the amount of actual damages recovered, defendant's financial condition and the probable litigation expenses. Ayers v. Christiansen, 222 Kan. 225, 229, 564 P.2d 458 (1977).' p. 694." 226 Kan. at 686.

In Restatement (Second) of Torts §908 (1977), we find the following:

> "(1) Punitive damages are damages, other than compensatory or nominal damages, awarded against a person to punish him for his outrageous conduct and to deter him and others like him from similar conduct in the future.
>
> "(2) Punitive damages may be awarded for conduct that is outrageous, because of the defendant's evil motive or his reckless indifference to the rights of others. In assessing punitive damages, the trier of fact can properly consider the character of the defendant's act, the nature and extent of the harm to the plaintiff that the defendant caused or intended to cause and the wealth of the defendant."

And see also Binyon v. Nesseth, 231 Kan. 381, 386, 646 P.2d 1043 (1982), affirming the Court of Appeals opinion in the same case, 7 Kan.App.2d 110, 638 P.2d 946 (1981); Kearney v. Kansas Public Service Co., 233 Kan. 492, 503, 665 P.2d 757 (1983); Ettus v. Orkin Exterminating

Co., 233 Kan.555, 567-68, 665 P.2d 730 (1983); Kline v. Multi-Media Cable-vision, Inc., 233 Kan. 988, 989, 666 P.2d 711 (1983) and Newton v. Hornblower, Inc., 224 Kan. 506, 524 -525, 582 P.2d 1136 1978).

The issue before us on this point is whether, viewed in the light most favorable to the plaintiff, there is evidence from which a jury could have found the defendant to be grossly negligent or recklessly indifferent to the rights of others.

Ortho is the manufacturer of a dangerous prescription drug Ortho-Novum 1/80. Therefore, Ortho is under a duty to make known to the medical profession,

or at least those physicians who are prescribing that drug, any of the dangerous side effects of which it knows or has reason to know. As the Oregon court observed in McEwen:

> "[T]he drug manufacturer is treated as an expert in its particular field, and is under a 'continuous duty * * * to keep abreast of scientific developments touching upon the manufacturer's product and to notify the medical profession of any additional side effects discovered from its use.' [Citations omitted.] The drug manufacturer's duty to warn is, therefore, commensurate not only with its actual knowledge gained from research and adverse reaction reports but also with its constructive knowledge as measured by scientific literature and other available means of communication." 270 Or. at 386.

The scientific evidence presented by the plaintiff disclosed that there were

twenty-one reported cases of women on oral contraceptives having HUS before the plaintiff presented that syndrome. At the time of trial there were some thirty-nine patient cases reported wherein oral contraceptives were associated with HUS. Nevertheless, there had never been a warning of any possible association between the use of Ortho-Novum 1/80 and HUS, malignant hypertension, vessel wall damage or acute renal failure contained within defendant's package inserts or within its PDR insertion. Even before plaintiff's renal failure, there were many articles in scientific journals linking oral contraceptives with these extremely serious conditions. As the Ohio Supreme Court noted in Seley:

> "[W]here scientific or medical evidence exists tending to show that a certain danger is associated with use of the drug, the manufacturer may not ignore or discount that information in drafting its warning solely because it finds it to be unconvincing." 67 Ohio St. 2d at 198. (Emphasis supplied.)

We agree, and we also think that the duty of the manufacturer must be commensurate with the seriousness of the danger. The greater the danger, the greater the duty.

One of the many documents in evidence is a "Dear Doctor" letter, sent nationally to all physicians by the acting commissioner of the Food and Drug Administration on January 12, 1970. The letter reads in part:

> "I am enclosing revised labeling for oral contraceptives to

reflect the latest findings on safety and efficacy, as reported by the Obstetrics and Gynecology Advisory Committee in August 1969. An American study confirms previously reported studies in Great Britain which show a relationship between the use of oral contraceptives and the occurrence of certain thromboembolic diseases. These carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than non-users. Studies in Great Britain also show increased risk of cerebral thrombosis and embolism in users of oral contraceptives. A British study found a hospitalization rate (an index of morbidity) in women age 20-44 to be 47 per 100,000 in users compared to five per 100,000 in non-users.

"The American study, although not designed to evaluate differences between products, also suggests there may be an increased risk of thromboembolic disease in users of sequential products. This difference in risk cannot be quantitated, and further studies are needed to confirm the observation.

> "The British Committee on Safety of Drugs recently advised practitioners in that country that only products containing 0.05 mg. or less of estrogen should normally be prescribed because reports of suspected adverse reactions indicated there is a higher incidence of thromboembolic disorders with products containing 0.075 mg. or more of estrogen than with products containing the smaller dose. This finding has not been confirmed by other studies.
>
> . . . .
>
> "I also request your assistance in continuing our assessment of the safety of oral contraceptives. Your reports of adverse reactions will help us to do this." (Emphasis supplied.)

Ortho-Novum 1/80 contains 80 micrograms (gammas) of estrogen, while Ortho-Novum 1/50 contains 50 micrograms of estrogen. On April 10, 1970, Ortho sent

a Sales Bulletin on the subject of Ortho-Novum labeling changes to its "detail men," sales representatives of the manufacturer who call directly upon physicians. That bulletin quoted extensively from the first paragraph of the acting commissioner's letter, but made no mention of the third paragraph concerning the British Committee's advice to physicians in England. On May 15, 1970, Ortho sent out another Sales Bulletin, this one on the subject of The Report of the British Committee on the Safety of Drugs. This bulletin did not quote the third paragraph of the acting commissioner's letter, but was obviously written in response thereto. It indicated that Ortho's own analysis of the British data indicates that there is no statis-

tically significant difference between 50, 75/80 and 100 micrograms of mestranol. It stated that products containing 75/80 gammas of mestranol show a risk as low if not lower than 50 gamma products. It urged the continued sale of its 80 gamma product, and cautioned its sales people not to be "stampeded" with the number 50. A July 6, 1970, Sales Bulletin continued to urge sale of Ortho-Novum 1/80, and urged concentration on Ortho-Novum 1/50 only if the physician "is very concerned with using lowest estrogen activity." For physicians who asked about switching patients to lower estrogen level products, the bulletin suggested the detail men respond:

> "Doctor, nothing in this British data offers enough sound evidence to

> cause you to switch patients who are on 100 gamma of mestranol. We have been saying for years and continue to say that it makes sense to use the least activity of any drug that will effectively accomplish its purpose; therefore, you may wish to move patients to low activity products such as ORTHO-NOVUM 1/80 or ORTHO-NOVUM 1/50."

In short, this evidence indicated that Ortho played down the British report and continued to urge sale of its higher estrogen product until Ortho itself could be entirely satisfied that the product was causing damage. Apparently its competitive position in the market was better served by continuing the manufacture and sale of its 1/80 product, since other manufacturers were also producing the 1/50 dosage.

Another area which plaintiff emphasizes is that of the "Irey-type" lesions. Dr. Nelson S. Irey, of the Armed Forces Institute of Pathology, issued a report in 1969, and published it in a pathology journal in 1970. The blood vessels of some forty women had been examined posthumously. Lesions were found in the inner wall or intima of the blood vessels of every one of the bodies of those women who were known to have been taking oral contraceptives; no such changes were found in the bodies of those who had <u>not</u> been taking oral contraceptives. In spite of this report linking oral contraceptives to vessel wall damage, Ortho did no further animal research to prove or disprove the proposition put forth by Irey: that oral contraceptives cause

vessel wall damage. The pathologist who examined plaintiff's kidney tissue found lesions to the intima or inner lining of the blood vessels in her kidneys remarkably similar to those lesions reported by Dr. Irey in his 1969 study.

We conclude that there was scientific and medical evidence tending to show that vessel wall damage, acute renal failure, malignant hypertension and HUS were extremely serious dangers which were associated with Ortho's product; that Ortho chose to ignore the accumulating medical and scientific evidence; that Ortho did not pursue the additional research which the data suggested; that Ortho continued to urge the use of its higher estrogen preparations, played down

the danger of those products, and gave physicians no warning of the dangers involved. From this evidence, the jury could have found that Ortho was grossly negligent and recklessly indifferent to the rights of others, including this plaintiff. The trial court did not err in submitting the issue of punitive damages to the jury.

Ortho argues that the mere submission of the punitive damage claim was so inflammatory and prejudicial that it requires that a new trial be granted on liability for compensatory damages. We have reviewed the court's instructions, the arguments of counsel and the court's ruling thereon, and find no error.

Ortho claims that the punitive damage award was so large as to shock the conscience. An award of $2,750,000 is, of course, enormous. The verdict of $2,000,000 for actual damages was also enormous. As we noted earlier in this opinion, Ortho does not challenge the award of actual damages; it does not argue that the $2,000,000 awarded as compensatory damages is excessive, or that the amount of that award is not supported by the evidence. The actual out-of-pocket medical expenses of the plaintiff were enormous; her injuries were enormous; and her injuries are continuing and permanent. The punitive damage award must be viewed in light of the actual damages sustained, the actual damage award, the circumstances of the

case, the evidence presented, the relative positions of the plaintiff and the defendant, and the defendant's financial worth. Upon a review of this record, we cannot find that an award of less than one and one-half times the actual damages as punitive damages is excessive.

Ortho also contends that the admission of evidence of its size and profits was error. We need not discuss this at length, however, for it is the rule in this state that the defendant's financial circumstances are relevant to the issue of punitive damages. See Ettus v. Orkin Exterminating Co., 233 Kan. 555, Syl. ¶ 7, 665 P.2d 730 (1983). The trial court did not err in admitting this evidence.

MITIGATING CIRCUMSTANCES and SUBSEQUENT REMEDIAL CONDUCT

Ortho argues that the trial court erred in refusing to permit Ortho to present evidence of "mitigating circumstances," and that the trial court erred in admitting evidence of "subsequent remedial conduct." We have reviewed the evidence targeted in these arguments and find no error. Ortho wished to introduce evidence of the benefits of oral contraceptives with regard to safety and effectiveness. There was much evidence in the record of the almost universal use of oral contraceptives, and no modern jury could be unaware of the widespread use and effectiveness and of the usual safety of oral contraceptives. The particular

evidence Ortho wished to introduce, however, was not evidence of "mitigating circumstances." That the product is widely used, ordinarily safe, and ordinarily effective, does not excuse the manufacturer's failure to warn of dangerous side effects of which the manufacturer knows or has reason to know. Evidence of widespread and beneficial use, and of usual safety and effectiveness, is not evidence of "mitigating circumstances," and the trial court did not err in excluding it.

The evidence of "subsequent remedial conduct" was not such as to come within that description. It was evidence of contacts between Ortho's Director of Medical Services and Dr. Diederich, fol-

lowing plaintiff's bout with HUS. Much of the discussions about which Ortho complains took place out of the hearing of the jury. The evidence admitted was offered only to show Ortho's continuing course of conduct--receipt of information linking high estrogen oral contraceptives with HUS, vessel wall damage, loss of kidneys, acute hypertension--and a continuing failure of Ortho to include warnings of these dangers to prescribing physicians or users of the products. We find no error in the admission of this evidence.

Finally, Ortho argues error in the admission or rejection of certain documentary evidence. This was a lengthy trial, carefully tried by able and

experienced counsel. We have carefully examined the record and find no prejudicial or reversible error. The judgment is affirmed.

SCHROEDER, C.J., dissenting: This is a comparative negligence action brought by the plaintiff Carol Lynn Wooderson, to recover damages for personal injuries which she claims resulted from ingestion of the oral contraceptive Ortho-Novum 1/80 over a period of years. The defendants named when the action was filed were the Ortho Pharmaceutical Corporation (Ortho) and the plaintiff's gynecologists, Dr. Hermes and Dr. Wilcox.

The plaintiff alleged negligence on the part of her doctors and on the part

of Ortho. When the pretrial conference was conducted the doctors were represented by counsel in the action and the plaintiff was pursuing her action against the doctors as well as Ortho.

After the pretrial conference and shortly prior to trial, the plaintiff settled with the two doctors who in turn moved for summary judgment which the trial court sustained. This court in its majority opinion gratuitously states, "a simple dismissal of plaintiff's claims, with prejudice, would have accomplished the same result." Ortho objected to the dismissal of the physicians, and at trial sought to have their negligence compared. The trial court ruled in substance that the negli-

gence of the doctors had been removed by counsel for the plaintiff from this action and the court was concerned only with questions raised by the plaintiff against the defendant Ortho.

This, in my opinion, was reversible error for the following reasons.

In its answer Ortho alleged that if the plaintiff sustained injury, she was guilty of negligence which contributed directly and proximately as a cause of her injuries, and that she failed to use the product in the manner intended. The answer of Ortho was also alleged that the plaintiff's injuries, if any, were caused by the negligence of other parties for whom Ortho is not responsible.

Addressing the comparative negligence statute, K.S.A. 60-258a, the court in its opinion says:

> "We have held that the intent and purpose of the legislature in adopting the statute is to impose individual liability for damages based on the proportionate fault of all of the parties to an occurrence which gave rise to the injuries and damages, whether or not those persons are joined formally as parties to the action." (Emphasis added.)

The court properly cites Brown v. Keill, 224 Kan. 195, 580 P.2d 867 (1978), for this proposition. However, from this point on in the opinion the court completely ignores Brown v. Keill without further comment on the validity of this precedent. Brown v. Keill was reaffirmed and asserted as controlling law on the

proposition above stated in Gaulden v. Burlington Northern, Inc., 232 Kan. 205, 654 P.2d 383 (1982). There a factual situation similar to the instant case was presented in a case involving the Federal Employers' Liability Act, 45 USCA § 51 et seq., (FELA). The plaintiff sued the railroad and Jack James. Later the plaintiff settled with James and the trial court dismissed James from the lawsuit. Even though the plaintiff was entitled to recover the entire judgment, less the plaintiff's percentage of negligence, from the railroad, the trial court was reversed and the case was sent back for a new trial with instructions that the neglilgence of James must be compared with that of the plaintiff and the railroad on the authority of Brown v. Keill,

and other cases cited therein. The court referred to the comparative negligence statute, K.S.A. 60-258a, and said:

> "The purpose of that statute is to impose individual liability for damages based upon proportionate fault. The concept of joint and several liability between joint tortfeasors no longer applies, and since individual judgments will be based upon proportionate fault, contribution among joint judgment debtors is no longer required. Brown v. Keill, 224 Kan. 195, 580 P.2d 867 (1978). . . .
>
> . . . .
>
> "We have consistently held that all issues of liability, including the causal negligence or fault of all parties to an occurrence, should be determined in one lawsuit, whether the participants are all formally joined as parties to that lawsuit or not. Brown v. Keill, 224 Kan. 195; Eurich v. Alkire, 224 Kan. 236, 579 P.2d 1207 (1978); Albertson v. Volkswagenwerk Aktiengesellschaft, 230 Kan. 368, 634 P.2d 1127 (1981); and Lester v. Magic Chef, Inc., 230 Kan. 643, 641 P.2d 353 (1982)." (Emphasis added.) 232 Kan. at 212-13.

In the case at bar, the trial court granted summary judgment for the doctors on their own motion, and ruled their negligence was no longer an issue. It then declared the sole remaining issue of negligence to be the adequacy of the warning given the doctors by Ortho in the distribution of its prescription drug, for which negligence if any, the plaintiff was entitled to recover damages. By this ruling the plaintiff was insulated at the trial against any charge of negligence.

By this procedure, and the instructions given by the trial court, Ortho was stymied. In substance, the jury was permitted to have only tunnel vision focused upon Ortho to respond for the total damages suffered by the plaintiff.

It cannot be successfully argued the doctors were not negligent in the administration of this prescription drug, or in their treatment of this young plaintiff, after her blood pressure in December 1974 was diagnosed by them as high, simply because the plaintiff settled with them. The plaintiff sued them charging negligence and pursued her claim against them. Only after settlement was a summary judgment sustained on the doctors' own motion.

The jury in this comparative negligence action should have been permitted to consider the negligence of all parties to the occurrence in order to fulfill the intent of the comparative negligence statute to impose individual liability

for damages based upon proportionate fault. See Gaulden v. Burlington Northern, Inc., 232 Kan. at 212-13.

For the court to declare, as a matter of law, that there was no evidence for the jury to consider on the issue of plaintiff's contributory negligence is presumptuous and speculative. The plaintiff, a young woman just married in 1972 and in good health, was diagnosed by her doctor as having high blood pressure (130/80) in December 1974, and again (120/90) in January 1976. She did not return to her doctor's office again until June 28, 1976, although she called in giving her symptoms on May 4, 1976, as a cold and on June 25, 1976, as stomach pains and vomiting. These facts in the

record must be viewed in light of a situation where the doctors have been erroneously removed from the case as parties whose negligence should have been considered. Had the case been tried with the doctors in the case for comparison of their negligence with that of the plaintiff and Ortho, the evidence may have been substantially different. The simple issue upon which the trial court admitted relevant evidence would have been expanded to other issues upon which evidence excluded would have been relevant.

By limiting the jury to the issue tried, the entire injury and resulting damages to the plaintiff were heaped upon Ortho. With the entire focus upon Ortho

and with the nature and extent of plaintiff's damages, it was not difficult for plaintiff's counsel to convince the jury to award substantial punitive damages. In fact, had the negligence of all parties been submitted to the jury the actual damages may have been much less and there may have been no punitive damages awarded.

It is respectfully submitted the judgment of the trial court should be reversed and a new trial granted in conformity with the law of comparative negligence as heretofore announced by the Supreme Court.

IN THE SUPREME COURT OF THE
STATE OF KANSAS

Carol Lynn Wooderson, Appellee,

v.

Ortho Pharmaceutical Corporation,
et al., Appellants.

You are hereby notified of the following action taken in the above entitled case:

Motion by Appellant for Rehearing.

Considered and Denied

Motion by Appellant Ortho Pharmaceutical Corporation pursuant to 28 U.S.C. § 2101(f) for stay of mandate and execution of judgment pending application to the Supreme Court of the United States for Writ of Certiorari.

Mandate is stayed until August 6, 1984, to allow defendant to petition for certiorari.

Yours very truly,

LEWIS C. CARTER
CLERK, SUPREME COURT

Date: June 25, 1984

APPENDIX B

APPENDIX B

STATUTES INVOLVED

§ 201(n) of the Federal Food, Drug and Cosmetic Act ("the Act"), 21 U.S.C. § 321:

> (n) If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling fails to reveal facts material in

> the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof or under such conditions of use as are customary or usual.

§ 502(a) and (n) of the Act, 21 U.S.C. § 352:

> A drug . . . shall be deemed to be misbranded (a) if its labeling is false or misleading in any particular
>
> . . .

(n) . . . In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of. . . (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with the procedure specified in section 371(e) of this title.

§ 505(a) and (d)(6) of the Act, 21 U.S.C. § 355:

> (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug. If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that . . . based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application.

MOTION FILED
SEP 19 1984

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No. 84-290

IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

v.

CAROL LYNN WOODERSON,
Respondent.

On Petition for a Writ of Certiorari To the Supreme Court of the State of Kansas

MOTION FOR LEAVE TO FILE BRIEF AMICUS CURIAE AND BRIEF AMICUS CURIAE OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION IN SUPPORT OF PETITION FOR A WRIT OF CERTIORARI

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September 19, 1984

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IN THE

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ORTHO PHARMACEUTICAL CORPORATION,

Petitioner,

v.

CAROL LYNN WOODERSON,

Respondent.

On Petition for a Writ of Certiorari
To the Supreme Court of the State of Kansas

MOTION OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION FOR LEAVE TO FILE BRIEF AMICUS CURIAE

The Pharmaceutical Manufacturers Association respectfully moves for leave to file the attached brief amicus curiae. The consent of the attorney for the petitioner has been obtained and filed with the Clerk, but respondent has refused consent.

PMA is a voluntary nonprofit association of 135 companies that are responsible for discovering, developing, manufacturing, obtaining Food and Drug Administration approval of, and selling almost all of the pioneer prescription new drugs in this country. Members of the association distribute prescription drugs, including oral contraceptives, in interstate commerce for sale throughout the country. These companies are subject to the new drug approval requirements and drug labeling

requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. §§ 301-392, and regulations issued thereunder by the FDA, 21 C.F.R. Parts 200-202, 300-361.

The decision of the Supreme Court of Kansas that petitioner Ortho Pharmaceutical Corporation asks this Court to review imposes punitive damages upon a pharmaceutical company on the ground that the labeling of the company's oral contraceptive product did not adequately warn of certain risks, even though the FDA did not include those warnings in the uniform labeling that it had written and prescribed for all oral contraceptives during the relevant time, and even though the FDA had refused to approve another manufacturer's requests to add the warnings to the labeling for its oral contraceptive products. The FDA is the federal agency charged by Congress with ensuring that the use of prescription drugs will be "safe" and "effective" under the conditions set forth in their labeling.

In subjecting the petitioner to liability for punitive damages, the Kansas Supreme Court has effectively imposed a state regulatory requirement for the labeling of oral contraceptive products, and has done so in a manner that frustrates a pervasive system of federal regulation of labeling for oral contraceptive products. The decision also imposes an enormous penalty, in the amount of $2.75 million in punitive damages, upon a pharmaceutical manufacturer for the very reason that the company's labeling from 1970-1974 consisted of the uniform labeling that was carefully considered and precisely written by the FDA, and from 1975 consisted of the uniform labeling with certain modifications approved by the FDA consistent with the product's "new drug" license.

On many other occasions and in many other cases, PMA has acted vigorously to protect the rights of its member companies and to express its views on important issues relating to federal regulation of prescription new drugs. PMA believes that the attached brief amicus curiae can make a contribution to the Court's decision whether to grant the petition for a writ of

certiorari in this case. PMA's amicus brief supplements and does not repeat the arguments presented in the petition for a writ of certiorari. The brief documents the pervasive federal regulation of drug labeling in general and the unusually active role of the FDA in prescribing labeling requirements for oral contraceptive products in particular. As PMA shows, the Kansas Supreme Court's decision imposing a state standard for oral contraceptive labeling is totally inconsistent with the federal regulatory scheme.

Accordingly, PMA moves for leave to file the attached brief amicus curiae.

Respectfully submitted,

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September 19, 1984

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

No. 84-290

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

v.

CAROL LYNN WOODERSON,
Respondent.

On Petition for a Writ of Certiorari
To the Supreme Court of the State of Kansas

BRIEF AMICUS CURIAE OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION IN SUPPORT OF PETITION FOR A WRIT OF CERTIORARI

INTEREST OF AMICUS CURIAE

The interest of amicus curiae Pharmaceutical Manufacturers Association in this case is described in the foregoing motion for leave to file. This brief is concerned only with the first question presented by the petitioner.

STATEMENT

The first oral contraceptive was approved for sale as a "new drug" by the federal Food and Drug Administration (FDA), under a "new drug application" (NDA) submitted to the agen-

cy, in June 1960.[1] After a few years, the FDA received reports that this oral contraceptive might be associated with certain thromboembolic conditions. Accordingly, throughout the 1960s, the FDA undertook close surveillance of adverse effects reported from the use of these products.[2]

Details of the FDA's surveillance of oral contraceptive effects and the resulting prescription by the agency of the labeling that must accompany oral contraceptive products are set forth in the Argument section (Part II). In brief summary, so far as pertinent to the decision below—that petitioner Ortho should have included in the labeling of its products warnings of possible effects of the drug in addition to those prescribed by the FDA—the facts are:

The FDA established uniform labeling for oral contraceptive products in 1967 and issued revised uniform labeling in 1968.[3] Labeling is a term of art in drug law. Insofar as prescription drugs are concerned, it refers not simply to the actual label on the bottle of pills that a patient buys from a pharmacist but to all written material supplied to prescribing physicians by drug manufacturers.[4] It also includes, as in the case of oral contraceptives beginning in 1970, pamphlets written in lay language to be given by a physician to the patients for whom he prescribes a drug (often called "patient package inserts").

In December 1969, when it was considering revising the uniform labeling for oral contraceptives, the FDA learned that the British Committee on Safety of Drugs had advised practi-

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[1] "Competitive Problems in the Drug Industry": Hearings Before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business, 91st Cong., 2d Sess., Pt. 16, at 6787 (1970) (hereafter "Nelson Hearings")(App. B, 32a). Pertinent parts of these Hearings are reproduced in Appendix B to this brief.

[2] Nelson Hearings 6787-88 (App. B, 31a-34a).

[3] Nelson Hearings 6788 (App. B, 33a-34a). The text of the 1968 uniform labeling appears in Appendix C to this brief.

[4] As defined by the statute, the term "labeling" includes all printed matter (1) upon the article or its container or (2) accompanying the article. 21 U.S.C. § 321(m). *See* 21 C.F.R. Parts 201, 202.

tioners to prescribe only products containing 0.05 milligrams (mg) or less of estrogen.[5] This committee acted on reports suggesting a relationship between the amount of estrogen in oral contraceptives and the incidence of thromboembolic disorders. The FDA considered the British report and action but deliberately did not include any mention of it in the revised uniform labeling for oral contraceptives that the agency issued in early 1970.[6] The FDA discussed the British report in a letter to physicians enclosing the revised labeling and said that it was planning studies to evaluate the accuracy of the findings.[7] Later that year the FDA specifically denied a request by an oral contraceptive manufacturer for permission to depart from the prescribed uniform labeling and include a reference to the British report and the comparative safety of higher and lower estrogen doses.[8] The FDA likewise did not include any reference to the British report when it prescribed a uniform patient package insert for oral contraceptives in June 1970.[9]

In 1974 and 1975, further studies confirmed the earlier finding that higher-dose estrogen products were associated with an increased incidence of thromboembolism.[10] Accordingly, Ortho (and some other companies) asked the FDA to approve the inclusion of a statement about this association in the labeling for their oral contraceptive products. The FDA approved Ortho's request to make this addition to its labeling in 1974, pursuant to a "supplemental" NDA, the agency's procedure for modifying the labeling of a drug that is subject to an NDA, 21 C.F.R. § 314.8.

Later, in December 1976, the FDA revised the uniform labeling for oral contraceptive products to include a statement

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[5] Nelson Hearings 6792 (App. B, 40a).

[6] Nelson Hearings 6792 (App. B, 40a-41a).

[7] The 1970 uniform labeling and "Dear Doctor" letter are reproduced in Appendix D to this brief.

[8] *See* Petition for a Writ of Certiorari, p. 7.

[9] 35 Fed. Reg. 9001 (June 11, 1970).

[10] *See* 41 Fed. Reg. 53630, 53635, 53638(ref. 3) (December 7, 1976).

that data from epidemiological studies "have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism," and a recommendation that new users of oral contraceptives should be started on lower estrogen-dose products.[11]

In this revised uniform labeling, the FDA also added a statement, in the adverse reactions section, that impaired renal function had been "reported in users of oral contraceptives, and the association [with contraceptive use] has been neither confirmed nor refuted."[12] Some of these reports included references in the medical literature to a rare kidney disorder called hemolytic uremic syndrome (HUS). Although the FDA was aware of reports about HUS,[13] it did not include any mention of this alleged side effect in its December 1976 uniform labeling for oral contraceptives. Even in 1982, when G.D. Searle & Co. requested approval from the FDA to include HUS as an adverse reaction on the labeling of its oral contraceptive products, the FDA denied approval.[14] In the agency's judgment, the criteria for including HUS as an "adverse reaction" in the labeling had not been met, even by 1982, because the reports of HUS were anecdotal, not based on well-controlled scientific studies in accordance with the statute and regulations. (*See infra* pp. 12-13)

From the fall of 1972 until June 1976, respondent Carol Lynn Wooderson took Ortho-Novum 1/80, an oral contraceptive

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[11] 41 Fed. Reg. 53630, 53634 (December 7, 1976) (revised labeling required by April 6, 1977); 43 Fed. Reg. 4223 (January 31, 1978) (additional revisions and final rule).

[12] 41 Fed. Reg. at 53638.

[13] *See* Petition for a Writ of Certiorari, p. 18.

[14] *See* Petition for a Writ of Certiorari, pp. 13, 18. Searle nonetheless persisted in the use of labeling for its products that included a statement about a possible association between HUS and the use of oral contraceptives. After Searle submitted additional information to the agency and requested reconsideration of the matter, the FDA in 1983 approved inclusion of HUS as an adverse reaction in the labeling of Searle's products. Searle's inclusion of an HUS statement in the labeling pending a final decision by the FDA to approve or reject the revised labeling is authorized by 21 C.F.R. § 314.8(d).

(0.08 mg estrogen) manufactured by petitioner Ortho. The labeling of petitioner's product from 1970 through 1974 consisted of the uniform labeling prescribed by the FDA in 1970. After 1974 it consisted of the uniform labeling plus a statement about a possible association between estrogen dose and increased risk of thromboembolism, a modification of the uniform labeling that was approved by the FDA under the federal "new drug" license for the product. In July 1976, Mrs. Wooderson was diagnosed as suffering from renal (kidney) failure and HUS.

After trial in a state court, the jury returned a verdict and the court entered a judgment for respondent and against petitioner Ortho for compensatory damages of $2 million and punitive damages of $2.75 million. The punitive damage award was based on Ortho's failure to warn in the product labeling that there was a risk of HUS from contraceptive use and, in the product labeling from 1970-1974, that higher-dose estrogen products had been found by the British Committee to be associated with a higher incidence of thromboembolic disorders.

The Supreme Court of Kansas upheld both the compensatory damages and the punitive damages awards. (App. A to the Petition.) The court upheld the imposition of punitive damages even though the FDA had not prescribed HUS or estrogen-dose warning statements for the uniform labeling of oral contraceptive products, and indeed had explicitly declined to authorize the inclusion of an HUS warning as late as 1982.

SUMMARY OF ARGUMENT

This case gives the Court an opportunity to decide an important question of federal law grounded in the Supremacy Clause of the Constitution and the comprehensive scheme for regulation of prescription new drugs in the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. §§ 352, 355. The decision below ignores that scheme and the FDA's singularly painstaking and detailed enforcement of it in its licensing and regulation of oral contraceptive products. The Kansas court premised an award of punitive damages on the failure to give warnings that

the FDA determined should *not* be included in the labeling of oral contraceptive products during the relevant time periods. The case thus poses issues that flow from this Court's recognition last term in *Silkwood* v. *Kerr-McGee Corp.*, 104 S. Ct. 615 (1984), that state tort remedies are subject to federal preemption if in their effect of prescribing standards that must be adhered to at the risk of being penalized by an award of punitive damages they conflict with federal law or stand as an obstacle to the accomplishment of Congressional objectives.

As an incident of its new-drug licensing authority, the FDA wrote uniform labeling to accompany oral contraceptives and approved modifications of the uniform labeling only when it believed that scientific evidence supported the addition of certain warnings or other statements to the labeling of such products. Fully aware of the studies that the Kansas court has decided should have been the subject of further warnings by petitioner, the FDA during the relevant time periods declined to require or approve the inclusion of such warnings in the labeling because the dangers were not substantiated. This action reflects the FDA's policy that to warn of unsubstantiated dangers is to risk obscuring real dangers in a mass of verbiage. The warnings that the Kansas court demands thus could not have been given by petitioner without the FDA's approval, consistent with the FDA's new-drug license for petitioner's oral contraceptive product and the agency's rules, and the Kansas court's insistence that they be given stands to thwart the FDA policy of stringent regulation of the labeling for oral contraceptives.

ARGUMENT

The decision below presents the important federal question whether punitive damage awards premised on a drug manufacturer's failure to give warnings that the responsible federal agency has not required or permitted in the federally prescribed or approved labeling of a drug (1) conflict with the comprehensive federal regulation of prescription drug labeling

and (2) frustrate the objective of the federal agency in establishing stringent regulation of the labeling for a particular class of drug products.

The Kansas Supreme Court authorized the imposition of punitive damages on the ground that the labeling of the manufacturer's oral contraceptive drug product did not contain certain label warnings, even though the warnings required under the state court's decision had been specifically rejected by the federal Food and Drug Administration during the relevant time periods. In refusing to defer to the federal regulatory scheme, the Kansas state courts have allowed the judgment of a lay jury to be substituted for that of the expert federal agency charged with ensuring that drug labeling contains the necessary information for the safe and effective use of drugs by consumers. This result conflicts with principles announced in prior decisions of this Court.

Last term, in *Silkwood* v. *Kerr-McGee Corp.*, 104 S. Ct. 615 (1984), this Court sustained an award of punitive damages under state tort law against a claim of preemption. In doing so, the Court nevertheless recognized that state tort remedies, including especially the remedy of punitive damages—the functional equivalent of regulatory fines for conduct that falls short of a regulatory prescription[15]—enjoy no special immunity from federal preemption. *San Diego Building Trade Council* v. *Garmon*, 359 U.S. 236 (1959). State tort remedies cannot validly be applied in respect of the subject of federal regulation when Congress has acted to displace state regulation by occupying a field, when state law "actually conflicts with federal law, that is, when it is impossible to comply with both state and federal law," or when "the state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress." 104 S. Ct. at 621. In *Silkwood* the company's only claim that was even colorable rested on occupation of the field, and that claim was refuted by Congress' manifested understanding that state tort remedies were available to victims of

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[15] *See* 104 S. Ct. at 625-26 (opinion of the Court); *id.* at 629-30 (dissenting opinion of Blackmun, J.); *id.* at 635 (dissenting opinion of Powell, J.).

nuclear accidents. *Id.* at 623-24. So far as the other possible bases of preemption were concerned, in *Silkwood* adherence to both a state and a federal standard of nuclear safety was not at all impossible even if the state standard was more demanding than the federal standard, and the imposition of a higher state standard did not stand in the way of the accomplishment of Congress' safety purposes and objectives but rather would serve them. *Id.* at 626.

In this case, to the contrary, apart from occupation of the field by pervasive federal regulation of prescription drugs marketed in interstate commerce, the kind of label warnings required by the Kansas court's decision had been specifically rejected by the FDA. Any oral contraceptive product "labeled" with any warning other than the warnings approved under the FDA's regulations would have been misbranded in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 331(a), 352(f), 355(e). It was therefore impossible for petitioner to comply with both the Kansas and the federal law concerning label warnings. Additionally, the Kansas law of drug label warnings presents a serious obstacle to the accomplishment of the federal objective of licensing and regulating the labeling of oral contraceptive products in the interest of the safety of their users.

I. The Federal Food, Drug, And Cosmetic Act And The Regulations Promulgated Under It Establish A Pervasive Federal System Of Rules To Govern Prescription Drug Labeling.

A. The Federal Food, Drug, and Cosmetic Act Establishes a Comprehensive Federal Scheme Regulating the Approval and Labeling of Prescription New Drugs.

The heart of the federal authority to regulate prescription drugs in the interest of safety lies in the provisions of the Federal Food, Drug, and Cosmetic Act dealing with new drugs. The Act prohibits the marketing in interstate commerce of a new drug, as defined in Section 201(p), 21 U.S.C. § 321(p), unless a new drug application (NDA) has been filed

for the drug and approved by the FDA under Section 505 of the Act, 21 U.S.C. § 355.[16] Generic copies of a previously approved pioneer new drug individually require their own approved NDAs.[17] This process of product licensure necessarily entails extensive agency involvement in the labeling of new drugs as well as in assessing their safety and effectiveness.[18] The FDA exercised this licensure authority when it approved the marketing of oral contraceptive drug products.

Section 505(b) of the Act specifies the information that must be submitted as part of an NDA. In addition to safety and effectiveness data, an NDA must contain "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b). Section 505(d) empowers the FDA to approve an NDA only if the drug has been shown to be safe and effective "under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof . . .." 21 U.S.C. § 355(d)(5). Furthermore, the FDA must disapprove an NDA if, "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular." *Id.* § 355(d)(6).

Under the new-drug approval process, the FDA must weigh a drug's therapeutic benefits against the potential risks from its use.[19] The FDA's decision whether to approve an NDA "also involves composing labeling to restrict the conditions for use

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[16] Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640 (1973); Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645 (1973); USV Pharmaceutical Corp. v. Weinberger, 412 U.S. 655 (1973).

[17] United States v. Generix Drug Corp., 103 S. Ct. 1298 (1983).

[18] To carry out its responsibility for ensuring that drugs are safe and effective, the FDA has promulgated an elaborate and complex set of regulations that define "new drugs," that govern the research and clinical investigations that must precede submission of an NDA, and that govern the submission, evaluation, and approval or disapproval of NDAs. 21 C.F.R. Parts 310, 312, 314, 320.

[19] "Drug Safety": Hearings Before the Subcomm. on Intergovernmental Relations of the House Comm. on Government Operations, 88th Cong., 2d Sess., Pt. 1, at 150, 153 (1964).

and thereby limit the risks of harm."[20] A former general counsel of the FDA has explained this process:[21]

> "The FDA not only decides whether a drug may be marketed, it also determines how it may be promoted and sold. The agency approves, and for practical purposes prescribes, the labeling that the drug must bear. . . . In this critical part of the approval process the FDA attempts to refine and articulate its initial weighing of hazards and benefits. It believes, and indeed tort law assumes, that the information conveyed by the labeling will effectively control the use of a drug and thereby limit risks and enhance benefits."

Licensing of the labeling is thus inherent in the FDA's licensing of the new drug.

In addition to using its licensing authority to prescribe drug labeling in advance, the FDA is responsible for regulating the labeling of prescription drugs once they are marketed. Section 502(f) of the Act requires that drug labeling must bear

> "(1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . .." 21 U.S.C. § 352(f).

If a drug fails to contain the required warnings, it is misbranded under the FD&C Act, thereby subjecting its manufacturer to potential civil and criminal penalties. *Id.* §§ 331-337, 352. Where information discovered after a drug is marketed indicates a need for additional warnings to physicians, the FDA will require changes in the approved labeling. If the labeling is not corrected within a reasonable time, the FDA is empowered to withdraw the NDA approval, thus revoking the license to market the drug. *Id.* § 355(e).

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[20] Merrill, *Compensation For Prescription Drug Injuries*, 59 Va. L. Rev. 1, 9 (1973).

[21] *Id.* at 11. The author is now dean of the University of Virginia Law School.

The FDA's function as the expert agency with primary jurisdiction over the resolution of all questions regarding the labeling of new drugs (and drugs in general) cannot be carried out if state courts, and indeed lay juries, are permitted to second-guess the scientific and policy decisions the FDA makes.[22]

B. The Food and Drug Administration Has Established a Comprehensive and Pervasive System of Drug Labeling Regulations.

Drawing on the authority of both the FD&C Act and the Fair Packaging and Labeling Act,[23] the FDA has established a comprehensive system of regulations to govern the labeling of drugs. The FDA's drug labeling regulations are detailed and particular. These rules govern as to all drugs such matters as the label declaration of the manufacturer or distributor, the use of National Drug Code numbers to identify manufacturers and products, adequate directions for use, statements of ingredients, prominence of required statements, use of lot control numbers, statements of identity, and statements of dosage.[24] Other rules govern specifically the content and format of labeling for human prescription drugs.[25] A specific rule governs potentially misleading statements in drug labeling.[26] Additionally, a series of regulations establish special labeling requirements for particular kinds of drug products.[27] In their application to prescription drugs, these requirements are in addition to those embodied in the FDA-approved NDA—the individual federal license described above that specifies in detail the manner in which a prescription drug must be manufactured and labeled.

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[22] *See* Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 653-54 (1973); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 627 (1973); Ciba Corp. v. Weinberger, 412 U.S. 640, 643-44 (1973).

[23] 15 U.S.C. § 1451 *et seq.*

[24] 21 C.F.R. §§ 201.1, 201.2, 201.5, 201.10, 201.15, 201.17, 201.18.

[25] 21 C.F.R. §§ 201.56, 201.57.

[26] 21 C.F.R. § 201.6.

[27] 21 C.F.R. §§ 201.300-201.317.

Section 201.57 of the FDA's regulations is entitled "specific requirements on content and format of labeling for human prescription drugs."[28] This regulation specifies in detail the circumstances in which reported adverse effects that might be associated with the use of a drug constitute "adverse reactions" that must be listed under that heading in the drug labeling. 21 C.F.R. § 201.57(g). As defined in the regulation, "an adverse reaction is an undesirable effect, reasonably associated with the use of the drug." *Id.* The FDA has construed "adverse reaction" as follows:

> "That definition would not include unsubstantiated reactions, disease symptoms, or apparently undesirable effects coincidental to the use of a drug, because they would not be reasonably associated with the use of the drug. . . . Accordingly, adverse effects and adverse experiences are not synonymous with adverse reactions and should not be included in prescription drug labeling." 44 Fed. Reg. 37434, 37453 (June 26, 1979).

Section 201.57 also governs the circumstances in which an adverse reaction rises to the level of a serious hazard that must be listed in the "warnings" section of the labeling. 21 C.F.R. § 201.57(e).

Where label statements are required under these standards, they must be made "in clear and unambiguous terms."[29] It was to ensure clear and concise warnings about *documented* hazards that the FDA promulgated its regulations requiring a specific format and content for prescription drug labeling:

> "[T]he law requires labeling to include warnings about both potential and verified hazards. Moreover, the law permits labeling statements with respect to safety only if they are supported by scientific evidence and are not false or misleading in any particular . . ..
>
> "Accordingly, labeling is not intended to be a dispositive treatise of all possible medical opinion about a drug. It is, instead, intended to advise about potential hazards and

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[28] This regulation is set forth in full in Appendix A to this brief.

[29] 39 Fed. Reg. 33229, 33231 (September 16, 1974).

convey documented statements with respect to safety and effectiveness." 40 Fed. Reg. 28582, 28583 (July 7, 1975).

When the available scientific evidence documents a reasonable association between the use of a drug and an adverse effect, the FDA requires the inclusion of that information in the drug labeling. If that required information is not included in the labeling, the FDA will not approve an NDA and the labeling for a new drug or will take regulatory action against a drug already on the market on the ground that it is misbranded under the Act. On the other hand, the FDA has determined that, when the scientific data do not document a "reasonable association" between the use of a drug and an adverse effect, such adverse effect "should not be included in prescription drug labeling." 44 Fed. Reg. at 37453.

The reason for this rule is obvious: If drug labeling contains too much information, it is less likely that any of the information will be absorbed by the prescribing physician.[30] A diffusion of warnings "would result in such uncertainty and confusion that the usefulness of such warnings in protecting the public against possible harm would be severely undermined, if not destroyed."[31] That is why a manufacturer must obtain the FDA's approval to include on a prescription drug "label" (or in other communications to physicians about the drug[32]) warnings about possible adverse effects that it knows about from experience or the literature, and why the FDA will not grant such approval if no "reasonable association" between the effect and use of the drug has been established.[33]

In keeping with these principles, the FDA has also issued regulations governing the circumstances in which comparative statements concerning safety of similar drug products may be made. Before drug labeling may include any statements comparing the relative safety, "either greater or less," of simi-

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[30] *See* 44 Fed. Reg. at 37453; 40 Fed. Reg. at 28583.

[31] 40 Fed. Reg. at 28583.

[32] 21 C.F.R. § 202.1.

[33] 21 C.F.R. § 314.8 (governing submission of a supplemental NDA by the manufacturer to propose and obtain approval of revised labeling).

lar drug products—such as the relative safety of high and low estrogen-dosage forms of oral contraceptive products—the statements must be supported by reliable scientific evidence. 21 C.F.R. § 201.57(c)(3)(v). Again, the purpose of this regulation is to avoid giving physicians erroneous or incomplete information concerning drug products.[34]

Despite this pervasive federal regulatory scheme, the Kansas Supreme Court has now authorized lay juries to substitute their judgment for that of the FDA in requiring, through the imposition of punitive damages, the inclusion in drug labeling of warnings of adverse effects that the FDA expressly determined to exclude from such labeling. It is inconceivable that 50 individual states can pick and choose among the rules that make up this comprehensive federal drug labeling scheme, or can require warnings based on the decisions of lay juries that are in addition to the warnings and labeling required by the expert federal agency, without interfering with the purpose of the federal drug law. Because state standards that impose drug labeling requirements that have been rejected by the FDA under federal law will frustrate the purposes of the FD&C Act, the federal requirements embodied in the FDA's labeling decisions must be given preemptive effect.

II. As An Incident Of Its New-Drug Licensing Authority Under The FD&C Act, The FDA Determined Not To Prescribe Or Approve The Label Warnings That Were Required Under The Standard Established By The Kansas Courts, And Thus The State Standard Is Preempted.

The award of punitive damages against petitioner Ortho was based on the fact that the labeling for its oral contraceptive product did not contain (1) a warning that HUS was a possible but unconfirmed side effect from use of oral contraceptives and (2) a statement, from 1970-1974, that higher estrogen dosage products might be associated with an increased risk of thromboembolic disorders based on the results of a British epidemiological survey conducted in 1969. To authorize an

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[34] 44 Fed. Reg. at 37441.

award of punitive damages on this basis is to disregard the FDA's express determinations that the HUS warning and the estrogen dosage relationship to thromboembolic disorders should *not* be included in oral contraceptive product labeling during the periods at issue here. In the FDA's judgment at that time, the available scientific evidence did not substantiate their inclusion. The conflict with federal authority is especially egregious because the FDA took a particular interest in oral contraceptives, played an active role in the studies of possible side effects, and even composed uniform labeling for oral contraceptive products.

The history of the agency's actions with respect to oral contraceptives was detailed by FDA Commissioner Edwards in 1970 before the Subcommittee on Monopoly of the Senate Select Committee on Small Business.[35] In his testimony, Commissioner Edwards outlined the FDA's "continued surveillance of adverse reactions" from the time the first oral contraceptive was approved in June 1960 through the British Committee's report on a suspected relationship of estrogen dosage to increased thromboembolic disorders in 1970, the report that the Kansas court considered crucial in imposing punitive damages upon petitioner.

The FDA's expert Advisory Committee on Obstetrics and Gynecology reviewed available scientific evidence on adverse effects of oral contraceptives and reported its conclusions to the agency in 1966 and again in 1969. The FDA funded studies of the effects of oral contraceptives on renal function, blood coagulation mechanisms, and other potential effects, including a study to determine the possible relationship of oral contraceptive use to thromboembolic disease.[36] The FDA established uniform physician labeling for all oral contraceptives in 1967 and monitored the labeling closely, revising it in 1968 and 1970. In 1970 it devised the concept of a "patient package

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[35] Nelson Hearings 6779-6837 (App. B). The pertinent parts of the testimony by Commissioner Edwards and Dr. Jennings of the FDA are set forth in Appendix B to this brief and summarized in the text.

[36] Nelson Hearings 6788 (App. B, 33a).

insert," which would provide information about risks and benefits of oral contraceptives in lay language directed to the user.[37] This was the first time that labeling directed to consumers had ever been required for an American prescription drug.[38]

In 1968, the results of epidemiological studies in Great Britain became available. After evaluating the data, the FDA concluded:

> "For the first time these studies demonstrated an increased incidence of thromboembolic disease in users of oral contraceptives. . . . Based on this conclusion, in June of 1968, FDA sent a letter to all physicians advising them of the British findings."[39]

Accompanying the FDA's 1968 "Dear Doctor" letter was the text of revised uniform labeling for oral contraceptives. That labeling contained information reflecting the results of the British studies.[40] The results of the British studies were confirmed by an American study published in August 1969. This study and other data regarding the use of oral contraceptives prompted the FDA in November 1969 to begin the process of changing the uniform labeling again.[41]

In December 1969, the FDA learned that the British Committee on Safety of Drugs had advised practitioners in that country "to prescribe only products containing .05 milligrams or less of estrogen."[42] This advice was based on reports suggesting the association of a higher incidence of thromboembolic disorders with oral contraceptive products containing .075 mg of estrogen or more. The FDA expressly determined not to include the British Committee report in the revised

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[37] 35 Fed. Reg. 9001 (June 11, 1970); 35 Fed. Reg. 5962 (April 10, 1970).

[38] "Regulatory Policies of the Food and Drug Administration": Hearing Before a Subcomm. of the House Comm. on Government Operations, 91st Cong., 2d Sess. 79 (June 9, 1970).

[39] Nelson Hearings 6788 (App. B, 34a).

[40] This letter appears in Appendix C to this brief. Source: Nelson Hearings, Pt. 17, 7022-25.

[41] Nelson Hearings 6792 (App. B, 39a).

[42] Nelson Hearings 6792 (App. B, 40a).

uniform labeling that it issued in 1970. Instead, the FDA decided to evaluate both the British data and the FDA's own data to determine whether the evidence justified a special warning or statement regarding products containing higher dosages of estrogen.[43] The FDA officials explained in their Congressional testimony that the process of evaluating the British data would be very complex, because it involved considerations of not only the safety of different estrogen dosages but also their effectiveness.[44] Thus, in the FDA's judgment, it would be inappropriate to single out products with more than .05 mg of estrogen for immediate regulatory action.

Accordingly, the FDA expressly decided *not* to include a warning or statement about a possible estrogen dosage relationship in the uniform labeling of oral contraceptive products in 1970. Instead, it notified prescribing physicians about the British Committee report by means of the "Dear Doctor" letter that accompanied the revised uniform labeling, and stated that the FDA was planning studies to determine the accuracy of the British finding.[45]

The uniform physician labeling required by the FDA in January 1970 therefore contained warnings about "an increased risk of thromboembolic disease associated with the use of hormonal contraceptives," but it did not include a statement about the British Committee's advice on low estrogen dosage products because any such statement would have the potential to mislead. Similarly, the FDA expressly refused to permit the drug manufacturer Searle to depart from the uniform labeling by adding a reference to the British report in the labeling for Searle's oral contraceptive products.[46] The FDA again declined

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[43] Nelson Hearings 6792 (App. B, 40a)(testimony of FDA Commissioner Edwards).

[44] Nelson Hearings 6793 (App. B, 41a-42a)(detailed explanation of the scientific and policy issues in the testimony of Dr. Jennings, Director of the FDA's Bureau of Medicine).

[45] The 1970 letter and revised uniform labeling appear in Appendix D. Source: Nelson Hearings, Pt. 17, 7017-21.

[46] *See* Petition for a Writ of Certiorari, p. 7.

to mention the British Committee's advice in June 1970 when it prescribed uniform patient labeling—the patient package insert—to inform users in lay language about the risks and benefits of oral contraceptives.[47]

The 1970 uniform labeling contained an adverse reaction statement about the possibility of increased blood pressure. The inclusion of this statement was based on the 1969 report of the FDA's Advisory Committee, concluding that this reaction had been established as occurring in users of oral contraceptives.[48] Although this report to the FDA mentioned the possibility of adverse effects on kidneys,[49] the FDA did not include such unsubstantiated effects in the 1970 uniform labeling. Nor were they included in the patient package insert required by the FDA later that year.

From 1970 through 1976, the FDA continued to conduct and fund studies of thromboembolic disorders, possible effects on kidney function, and other possible effects of oral contraceptives.[50] In 1975, the FDA issued press releases announcing new information on potential risks of oral contraceptives[51] and revised the patient package insert to include information about venereal disease.[52] In October 1975, the FDA also began to solicit comments on revised physician labeling for oral contraceptives.[53]

It was not until December 1976 that the FDA revised both the physician and patient labeling—required to be uniform for all oral contraceptive products, except for modifications approved by the FDA under the individual new-drug licenses—to include a statement that "epidemiological studies have

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[47] 35 Fed. Reg. 9001 (June 11, 1970).

[48] Nelson Hearings, Pt. 17, 6903. The Advisory Committee's Report is reproduced in Nelson Hearings, Pt. 17, 6839-6915.

[49] Nelson Hearings, Pt. 17, 6904.

[50] Nelson Hearings 6794 (App. B, 43a-45a)(discussing studies in progress).

[51] *See, e.g.*, "FDA Talk Paper," T75-67 (October 16, 1975).

[52] 40 Fed. Reg. 48918 (October 20, 1975).

[53] 40 Fed. Reg. 49813 (October 24, 1975).

shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism."[54] Even in this revised labeling, the FDA did not mention any association between the use of oral contraceptives and an increased risk of HUS. The omission of an HUS warning was significant. In its "continued surveillance" of adverse effects that might be associated with the use of oral contraceptives, the FDA knew of anecdotal reports of HUS in some users of oral contraceptives.[55] The agency believed that there was no evidence of a reasonable association between HUS and the use of oral contraceptives and, therefore, no HUS warning was required as a part of the uniform labeling. This remained the FDA's position in 1982 when it rejected a request by Searle to depart from the uniform labeling and include HUS as an adverse reaction in the labeling for Searle's products.[56]

Despite all this, the Kansas Supreme Court's decision holds that lay juries can substitute their judgment for that of the FDA with regard to the important scientific and policy decisions that underlie the content of drug labeling. The punitive damage award authorized by that decision will penalize a drug manufacturer who was *required by law* to conform the labeling for its oral contraceptive products to either the uniform labeling prescribed by the FDA or the uniform labeling with modifications approved by the FDA pursuant to its new-drug licensing authority under the FD&C Act. It is obvious that, if allowed to stand, the Kansas Supreme Court's decision will completely frustrate the purposes of the federal regulatory scheme and the FDA's especially close regulation of the labeling of oral contraceptive products.

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[54] 41 Fed. Reg. 53633, 53634 (December 7, 1976).

[55] *See* Petition for a Writ of Certiorari, p. 18. *See also* 21 C.F.R. §§ 310.300, 310.301 (requiring reporting to the FDA of studies and adverse drug experiences).

[56] *See supra* note 14.

CONCLUSION

For the reasons set forth above, the petition for a writ of certiorari should be granted.

Respectfully submitted,

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APPENDIX A

Specific Requirements On Content And Format Of Labeling For Human Prescription Drugs, 21 C.F.R. § 201.57

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Specific Requirements On Content And Format Of Labeling For Human Prescription Drugs, 21 C.F.R. § 201.57

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§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

Each section heading listed in § 201.56(d), if not omitted under §§ 201.56(d)(3), shall contain the following information in the following order:

(a) "Description":

(1) Under this section heading, the labeling shall contain:

(i) The proprietary name and the established name, if any, as defined in section 502(e)(2) of the act, of the drug;

(ii) The type of dosage form and the route of administration to which the labeling applies;

(iii) The same qualitative and/or quantitative ingredient information as required under § 201.100(b) for labels;

(iv) If the product is sterile, a statement of that fact;

(v) The pharmacological or therapeutic class of the drug;

(vi) The chemical name and structural formula of the drug;

(vii) If the product is radioactive, a statement of the important nuclear physical characteristics, such as the principal radiation emission data, external radiation, and physical decay characteristics.

(2) If appropriate, other important chemical or physical information, such as physical constants, or pH, shall be stated.

(b) "Clinical Pharmacology":

(1) Under this section heading, the labeling shall contain a concise factual summary of the clinical pharmacology and ac-

tions of the drug in humans. The summary may include information based on in vitro and/or animal data if the information is essential to a description of the biochemical and/or physiological mode of action of the drug or is otherwise pertinent to human therapeutics. Pharmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption, pathways of biotransformation, percentage of dose as unchanged drug and metabolites, rate or half-time of elimination, concentration in body fluids associated with therapeutic and/or toxic effects, degree of binding to plasma proteins, degree of uptake by a particular organ or in the fetus, and passage across the blood brain barrier. Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug. If the pharmacological mode of action of the drug is unknown or if important metabolic or pharmacokinetic data in humans are unavailable, the labeling shall contain a statement about the lack of information.

(2) Data that demonstrate activity or effectiveness in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use may be included under this secton of the labeling only under the following circumstances:

(i) In vitro data for anti-infective drugs may be included if the data are immediately preceded by the statement "The following in vitro data are available but their clinical significance is unknown."

(ii) For other classes of drugs, in vitro and animal data that have not been shown by adequate and well-controlled clinical studies, as defined in § 314.111(a)(5)(ii) of this chapter, to be pertinent to clinical use may be used only if a waiver is granted under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(c) "Indications and Usage":

(1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2) All indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless the requirements is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless the require-

ment is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(d) "Contraindications": Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use

of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) "Warnings": Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

(f) "Precautions": Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General: This subsection of the labeling shall contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug, e.g., precau-

tions not required under any other specific section or subsection of the labeling.

(2) Information for patients: This subsection of the labeling shall contain information to be given to patients for safe and effective use of the drug, e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects. Any printed patient information required under this chapter to be distributed to the patient shall be referenced under the "Precautions" section of the labeling and the full text of such patient information shall be reprinted at the end of the labeling.

(3) Laboratory tests: This subsection of the labeling shall identify any laboratory tests that may be helpful in following the patient's response or in identifying possible adverse reactions. If appropriate, information shall be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be done before, during, and after therapy.

(4)(i) Drug interactions: This subsection of the labeling shall contain specific practical guidance for the physician on preventing clinically significant drug/drug and drug/food interactions that may occur in vivo in patients taking the drug. Specific drugs or classes of drugs with which the drug to which the labeling applies may interact in vivo shall be identified, and the mechanism(s) of the interaction shall be briefly described. Information in this subsection of the labeling shall be limited to that pertaining to clinical use of the drug in patients. Drug interactions supported only by animal or in vitro experiments may not ordinarily be included, but animal or in vitro data may be used if shown to be clinically relevant. Drug incompatibilities, i.e., drug interactions that may occur when drugs are mixed in vitro, as in a solution for intravenous administration, shall be discussed under the "Dosage and Administration" section of the labeling rather than under this subsection of the labeling.

(ii) Drug/laboratory test interactions: This subsection of the labeling shall contain practical guidance on known interference of the drug with laboratory tests.

(5) Carcinogenesis, mutagenesis, impairment of fertility: This subsection of the labeling shall state whether long-term studies in animals have been performed to evaluate carcinogenic potential and, if so, the species and results. If reproduction studies or other data in animals reveal a problem or potential problem concerning mutagenesis or impairment of fertility in either males or females, the information shall be described. Any precautionary statement on these topics shall include practical, relevant advice to the physician on the significance of these animal findings. If there is evidence from human data that the drug may be carcinogenic or mutagenic or that it impairs fertility, this information shall be included under the "Warnings" section of the labeling. Also, under "Precautions," the labeling shall state: "See 'Warnings' section for information on carcinogenesis, mutagenesis, and impairment of fertility."

(6) Pregnancy: This subsection of the labeling may be omitted only if the drug is not absorbed systemically and the drug is not known to have a potential for indirect harm to the fetus. For all other drugs, this subsection of the labeling shall contain the following information:

(i) *Teratogenic effects.* Under this heading the labeling shall identify one of the following categories that applies to the drug, and the labeling shall bear the statement required under the category:

(a) *Pregnancy category A.* If adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category A. Studies in pregnant women have not shown that (*name of drug*) increases the risk of fetal abnormalities if administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. If this drug is used during pregnan-

cy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies. If animal reproduction studies are available and they fail to demonstrate a risk to the fetus, the labeling shall also state: "Reproduction studies have been performed in (*kinds of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*)." The labeling shall also contain a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(b) *Pregnancy category B.* If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, the labeling shall state: "Pregnancy Category B. Reproduction studies have been performed in (*kind(s) of animal(s)*) at doses up to (*x*) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (*name of drug*). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling shall state: "Pregnancy Category B. Reproduction studies in (*kind(s) of animal(s)*) have shown *(describe findings)* at (*x*) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(*s*) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the

studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed." The labeling shall also contain a description of the human studies and a description of available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(c) *Pregnancy category C.* If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: "Pregnancy Category C. (*Name of drug*) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (*name(s) of species*) when given in doses (*x*) times the human dose. There are no adequate and well-controlled studies in pregnant women. (*Name of drug*) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The labeling shall contain a description of the animal studies. If there are no animal reproduction studies and no adequate and well-controlled studies in humans, the labeling shall state: "Pregnancy Category C. Animal reproduction studies have not been conducted with (*name of drug*). It is also not known whether (*name of drug*) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (*Name of drug*) should be given to a pregnant woman only if clearly needed." The labeling shall contain a description of any available data on the effect of the drug on the later growth, development, and functional maturation of the child.

(d) *Pregnancy category D.* If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the

labeling states: "(*Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.*) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(e) *Pregnancy category X.* If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling shall state: "Pregnancy Cagetory X. See 'Contraindications' section." Under "Contraindications," the labeling shall state: "(*Name of drug*) may (*can*) cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinant animal data.*) (*Name of drug*) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

(ii) *Nonteratogenic effects.* Under this heading the labeling shall contain other information on the drug's effects on reproduction and the drug's use during pregnancy that is not required specifically by one of the pregnancy categories, if the information is relevant to the safe and effective use of the drug. Information required under this heading shall include nonteratogenic effects in the fetus or newborn infant (for example, withdrawal symptoms or hypoglycemia) that may occur because of a pregnant woman's chronic use of the drug for a preexisting condition or disease.

(7) Labor and delivery: If the drug has a recognized use during labor or delivery (vaginal or abdominal delivery), whether or not the use is stated in the indications section of the labeling, this subsection of the labeling shall describe the available information about the effect of the drug on the mother and

the fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary, and the effect of the drug on the later growth, development, and functional maturation of the child. If any information required under this subsection is unknown, this subsection of the labeling shall state that the information is unknown.

(8) Nursing mothers:

(i) If a drug is absorbed systemically, this subsection of the labeling shall contain, if known, information about excretion of the drug in human milk and effects on the nursing infant. Pertinent adverse effects observed in animal offspring shall be described.

(ii) If a drug is absorbed systematically and is known to be excreted in human milk, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or if the drug has a known tumorigenic potential, the labeling shall state: "Because of the potential for serious adverse reactions in nursing infants from *(name of drug)* (or, "Because of the potential for tumorigenicity shown for *(name of drug)* in *(animal or human)* studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "Caution should be exercised when *(name of drug)* is administered to a nursing woman."

(iii) If a drug is absorbed systemically information on excretion in human milk is unknown, this subsection of the labeling shall contain one of the following statements, as appropriate. If the drug is associated with serious adverse reactions or has a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants

from *(name of drug)* (or, "Because of the potential for tumorigenicity shown for *(name of drug)* in *(animal or human)* studies), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother." If the drug is not associated with serious adverse reactions and does not have a known tumorigenic potential, the labeling shall state: "It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *(name of drug)* is administered to a nursing woman."

(9) Pediatric use: A specific pediatric indication, if any, shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage shall be stated under the "Dosage and Administration" section of the labeling. Statements on pediatric use of the drug for an indication approved for adults shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is waived under § 201.58 or § 314.111(a)(5)(ii) of this chapter. If the requirements of § 314.111(a)(5)(ii) of this chapter cannot be met, this section of the labeling shall contain one of the following statements: "Safety and effectiveness in children have not been established," or "Safety and effectiveness in children below the age of (____) have not been established." If use of the drug in premature or neonatal infants, or in older children, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling; or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection of the labeling shall refer to it.

(g) "Adverse Reactions": An adverse reaction is an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence.

(1) This section of the labeling shall list the adverse reactions that occur with the drug and with drugs in the same

pharmacologically active and chemically related class, if applicable.

(2) In this listing, adverse reactions may be categorized by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate. If frequency information from adequate clinical studies is available, the categories and the adverse reactions within each category shall be listed in decreasing order of frequency. An adverse reaction that is significantly more severe than the other reactions listed in a category, however, shall be listed before those reactions, regardless of its frequency. If frequency information from adequate clinical studies is not available, the categories and adverse reactions within each category shall be listed in decreasing order of severity. The approximate frequency of each adverse reaction shall be expressed in rough estimates or orders of magnitude essentially as follows: "The most frequent adverse reaction(s) to *(name of drug)* is (are) *(list reactions)*. This (these) occur(s) in about (e.g., one-third of patients; one in 30 patients; less than one-tenth of patients). Less frequent adverse reactions are *(list reactions)*, which occur in approximately (e.g., one in 100 patients). Other adverse reactions, which occur rarely, in approximately (e.g., one in 1,000 patients), are *(list reactions)*." Percent figures may not ordinarily be used unless they are documented by adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter, they are shown to reflect general experience, and they do not falsely imply a greater degree of accuracy than actually exists.

(3) The "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction.

(4) Any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in § 314.111(a)(5)(ii) of this chapter unless this requirement is wavied under § 201.58 or § 314.111(a)(5)(ii) of this chapter.

(h) "Drug Abuse and Dependence": Under this section heading, the labeling shall contain the following subsections, as appropriate for the drug:

(1) Controlled Substance: If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled shall be stated.

(2) Abuse: This subsection of the labeling shall be based primarily on human data and human experience, but pertinent animal data may also be used. This subsection shall state the types of abuse that can occur with the drug and the adverse reactions pertinent to them. Particularly susceptible patient populations shall be identified.

(3) Dependence: This subsection of the labeling shall describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and shall identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details shall be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state shall be provided, and the principles of treating the effects of abrupt withdrawal shall be described.

(i) "Overdosage": Under this section heading; the labeling shall describe the signs, symptoms, and laboratory findings of acute overdosage and the general principles of treatment. This section shall be based on human data, when available. If human data are unavailable, appropriate animal and in vitro data may be used. Specific information shall be provided about the following:

(1) Signs, symptoms, and laboratory findings associated with an overdosage of the drug.

(2) Complications that can occur with the drug (for example, organ toxicity or delayed acidosis).

(3) Oral LD_{50} of the drug in animals; concentrations of the drug in biologic fluids associated with toxicity and/or death; physiologic variables influencing excretion of the drug, such as

urine pH; and factors that influence the dose response relationship of the drug, such as tolerance. The pharmacokinetic data given in the "Clinical Pharmacology" section also may be referenced here, if applicable to overdoses.

(4) The amount of the drug in a single dose that is ordinarily associated with symptoms of overdosage and the amount of the drug in a single dose that is likely to be life-threatening.

(5) Whether the drug is dialyzable.

(6) Recommended general treatment procedures and specific measures for support of vital functions, such as proven antidotes, induced emesis, gastric lavage, and forced diuresis. Unqualified recommendations for which data are lacking with the specific drug or class of drugs, especially treatment using another drug (for example, central nervous system stimulants, respiratory stimulants) may not be stated unless specific data or scientific rationale exists to support safe and effective use.

(j) "Dosage and Administration": This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules. Radiation dosimetry information shall be stated for both the patient receiving a radioactive drug and the person administering it. This section shall also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed, e.g., the rate of administration of parenteral drug in milli-

grams per minute; storage conditions for stability of the drug or reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs; and the following statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

(k) "How Supplied": This section of the labeling shall contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. The information shall ordinarily include:

(1) The strength of the dosage form, e.g., 10-milligram tablets, in metric system and, if the apothecary system is used, a statement of the strength is placed in parentheses after the metric designation;

(2) The units in which the dosage form is ordinarily available for prescribing by practitioners, e.g., bottles of 100;

(3) Appropriate information to facilitate identification of the dosage forms, such as shape, color, coating, scoring, and National Drug Code; and

(4) Special handling and storage conditions.

(l) "Animal Pharmacology and/or Animal Toxicology": In most cases, the labeling need not include this section. Significant animal data necesssary for safe and effective use of the drug in humans shall ordinarily be included in one or more of the other sections of the labeling, as appropriate. Commonly for a drug that has been marketed for a long time, and in rare cases for a new drug, chronic animal toxicity studies have not been performed or completed for a drug that is administered over prolonged periods or is implanted in the body. The unavailability of such data shall be stated in the appropriate section of the labeling for the drug. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this section may be used.

(m) "Clinical Studies" and "References": These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the "Clinical Studies" or "References" section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning an indication for the use of the drug, the reference shall be based upon, or the clinical study shall constitute, an adequate and well-controlled clinical investigation under § 314.111(a)(5)(ii) of this chapter.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.

(Secs. 502, 503, 505, 506, 507, 701, 52 Stat. 1050-53 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 355, 356, 357, 371); sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262))

[44 FR 37462, June 26, 1979]

APPENDIX B

Testimony (Partial) of FDA Commissioner Edwards Before The Subcommittee On Monopoly, Senate Select Committee On Small Business (March 4, 1970)

APPENDIX B

Testimony (Partial) Of FDA Commissioner Edwards Before The Subcommittee On Monopoly, Senate Select Committee On Small Business (March 4, 1970) (6779)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition In the Pharmaceutical Industry)

WEDNESDAY, MARCH 4, 1970

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 318, Old Senate Office Building, Hon. Gaylord Nelson (Chairman of the Subcommittee) presiding.

Present: Senators Nelson, McIntyre, and Dole.

Also present: Benjamin Gordon, Staff Economist; Elaine C. Dye, Clerical Assistant; James P. Duffy III, Minority Counsel; and Dennison Young, Jr., Associate Minority Counsel.

Senator NELSON. Our witness today is Dr. Charles Edwards, Commissioner, Food and Drug Administration.

Dr. Edwards, the committee is very pleased to have you appear here today. Your statement will be printed in full in the record.

You may present it as you desire, and if you wish to extemporize from it at any time, or elaborate on it, feel free to do so.

I assume you do not mind if we interrupt with questions as you go along.

Dr. EDWARDS. Not at all.

Senator NELSON. All right, go ahead, Doctor.

STATEMENT OF DR. CHARLES C. EDWARDS, COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. JOHN JENNINGS, DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; WILLIAM W. GOODRICH, GENERAL COUNSEL, FOOD AND DRUG ADMINISTRATION; AND DR. JOHN SCHROGIE, FOOD AND DRUG ADMINISTRATION

Dr. EDWARDS. Thank you, Senator Nelson, Senator Dole.

I would like to begin by introducing my colleagues. On my right, Dr. John Jennings, who is Director of the Bureau of Drugs, and on my left is Mr. William Goodrich, who is the general counsel for the Food and Drug Administration.

We certainly appreciate this opportunity to present to the committee the views of the Food and Drug Administration on some of the issues raised during these hearings. The primary issue, as we see it, has been the relative safety or oral contraceptives and a concern for public understanding of the risks associated with them. (6780)

We have, needless to say, carefully followed the progress of these hearings. You have heard a wide range of opinion concerning the safety of oral contraceptives. The opinions of these witnesses have been expressed intelligently and sincerely. They certainly merit serious consideration, both by you and by the Food and Drug Administration.

However, the expression of an informed opinion is not the same as making a decision. We, in the Food and Drug Administration, also have expert opinions; but it is our responsibility to study the available scientific data, consider the advice of our consultants and render a decision on the safety and efficacy of new drugs under the Federal Food, Drug, and Cosmetic Act.

At this point I wish to summarize the Food and Drug Administration's current position. I would like to emphasize

"current", because this is a situation that can change from month to month, year to year. However, our position is that the oral contraceptives are an effective and safe method of birth control, but as with other potent drugs there are both contraindications and complications.

Women whose history and present medical condition include thromboembolic disorders, impaired liver function, known or suspected cancer of the breast, estrogen dependent tumors, and abnormal bleeding should not take oral contraceptives.

Senator NELSON. Doctor, may I ask a question at this point?

Dr. EDWARDS. You certainly may.

Senator NELSON. On the use of the word "safe" in respect to the oral contraceptives, I think that there is considerable confusion within the medical profession and the public alike as to how the word "safe" was being used when the Hellman committee came to that conclusion and used the phrase "Safe within the intent of the law."

I would just like to read to you what Dr. Hellman said before the committee, and ask for your comment on it. I shall read out of context a couple of excerpts of his testimony.

This is Dr. Hellman speaking when he appeared before the committee—

> It is quite apparent if you read the report, in the first report the committee recognized certain very serious problems with oral contraceptives. They, however, were unwilling, and rightfully, I believe, to say these things ought to come off the market.

Now, I skip down further where Dr. Hellman states:

> Now, in discussing the Chairman's report, the second report, with the committee, I said to them that a more forthright statement has to be made. We cannot just hide behind rhetoric, we are going to have to say something and we have an option. These are not safe and then the commissioner might have to take them off the market, if you believe this. We can say these are safe, and our scientific data really did not permit that kind of statement.

I doubt whether one doctor in 10,000 in the country knows that this was what Dr. Hellman, the Chairman, said and understands the context within which the word "safe" was used in reaching the conclusion when the Chairman of FDA's Advisory Committee said "safe within the meaning of the intent of the law."

Would you mind elaborating on that? (6781)

Dr. EDWARDS. Certainly. In categorizing this drug as safe, I do not want to imply, by any stretch of the imagination, that this is an innocuous drug. It is a very potent drug, and when arriving at this decision to call it a safe drug we had to utilize the same standards we use for all other drugs.

As you well know, most of the other "safe" drugs, the powerful drugs, have certain contraindications. There are certain dangers in taking any drug, and they have to be taken under the conditions which are stated very clearly in the labeling.

So again, I would like to emphasize that in establishing this classification, we applied the same standards for the oral contraceptives as we have for all other drugs in categorizing them as safe.

Senator NELSON. The use in this context, then, was not in the ordinary dictionary use of the word—

Dr. EDWARDS. It certainly was not. It was a Food and Drug Administration description of the word "safe", which really is "safe under the conditions of labeling," and which perhaps is a more accurate definition.

Senator NELSON. This is a legal question. Dr. Hellman mentioned that he discussed the phrasing—do you have Dr. Hellman's phrasing?

In any event, he discussed how it should be phased with your counsel, Mr. Goodrich. Perhaps you may wish Mr. Goodrich to respond to this. But it raises another question of some significance, it seems to me.

Dr. Hellman said:

> Now, it therefore wrote the sentence that has caused you and Mr. Gordon and other people some difficulty. I take full responsibility for writing this sentence "safe within the intent of the legislation." But I did have consultation in writing the sentence.

And so forth, and he refers to your counsel, Mr. Goodrich.

If it had been my responsibility, I might have come to the same conclusion, but it does raise a question about the intent of the law and its meaning.

In 1938 Congress passed the statute requiring that to market a drug proof of safety must be submitted, adequate proof of safety or proof of safety acceptable to the FDA must be presented.

I would just like to ask Mr. Goodrich what he thinks was intended at that time. Let me state it this way:

In 1938 there were no oral contraceptives. In 1938, I would assume that the Congress was thinking of a drug for treatment of a specific target organism in a specific disease situation. In fact, it was in response to a particular safety problem that arose at that time respecting sulfanilamide, and maybe Mr. Goodrich will have a different view—and correct me if you do—that Congress was thinking then of a drug in which the issue was, is it safe for the particular disease situation which it is being used for, that is, the drug does have side effects, we are well aware of that; however, under the circumstance the illness of the patient indicates that on balance the risks of the side effects from the use of the drug are far outweighed by the benefits that the patient would get from the use of the drug for the particular disease situation that exists. (6782)

And just to delineate it a little further, let us take the case of chloramphenicol on which we had substantial hearings. This is a very potent drug and everybody knows it. It has in a certain incidence, some dramatic side effects involving blood dyscrasias, including aplastic anemia.

In today's circumstance, chloramphenicol, according to the National Research Council of the National Academy of Science, is not the drug of choice in any disease. It is the choice only when the target organism is subject to control by chloramphenicol, when no other drug will do the job, and when the disease situation is very serious.

So clearly, if you had some disease organisms that would not respond to treatment by tetracycline or any other drug, and the patient was seriously ill and the target organism was sensitive to chloramphenicol, the drug under that situation is safe within the meaning of the law.

However, if the disease is subject to treatment by tetracycline, it is not safe within the meaning of the law or if the patient has a serious disease or if the target organism is not subject to control by chloramphenicol, it is unsafe.

Is that your understanding of what the law means?

Mr. GOODRICH. Yes. My understanding is that all safety decisions have to be made in the context of the conditions for which the drug is prescribed, recommended or suggested.

Now, going back to what Congress had in mind in 1938 when they focused on an acute episode of poisoning, it happened to be due to the vehicle and not the drug itself. But as soon as we began passing on safety from the very first drug, the sulfanilamides, that were involved there, those drugs were not safe in any absolute sense of the term but they were quite safe in treating infectious disease at that time, because many of those were life threatening.

Now, in that class of drugs, of course, it is relatively easy to balance benefit-to-risk, which is the test here. But there are other types of drugs that we have had to deal with over the years, drugs used for prophylaxis, or that type of drug, and in each instance it is essential that the agency balance benefit to risk, because there are very few drugs that have no side effects whatever, if they do anything.

There are some innocuous drugs that do not do anything, but if they are innocuous, then they do not have any benefit or any risk; they are just ineffective.

But from the beginning of time we had to deal with the sulfanilamides, first as a class, with the corticosteroids, and many other classes of drugs that came on the market after 1938. And this was really kind of the beginning of a new era of chemotherapy that had both beneficial effects and side effects and contraindications that were necessary to be observed in using the drug.

Now, you had drugs effective against specific target organisms and effective as prophylactic measures.

Senator NELSON. Let me ask this question, though. Is it not correct when using the word "safe" that you do not mean safe in general, you mean safe for this particular patient who has a particular disease situation which the doctor decides that this drug will effectively treat, that is, target organism is subject to control by this drug, and on balance it is better that the patient risk whatever side effect this drug has rather than risk letting the disease run its course untreated by any drug. (6783)

It is an individual case, an individual disease, an individual prescription under an individual circumstance; is that not what we mean by "safe"?

Mr. GOODRICH. That is the decision for the individual prescriber, but the decision for the Food and Drug Administration has to take into account different circumstances in which the drug will be used, some in private practice, others in university medical centers.

It has to take into account the total experience with the drug in the total prescribing population, and make a judgment there on all of these circumstances, this drug will be reasonably safe, that is, its benefits outweigh its risk under the circumstances in which it enters the market.

There have been a few instances in which drugs were allowed to enter the market only for use in university-type

hospital settings, but in others the drug is permitted for widespread prescribing in most instance. But the Food and Drug decision has to take into account all of these circumstances in reaching a safety decision.

Senator NELSON. Maybe I am not making myself clear. When you say "safe within the meaning of the law" are you not saying that we mean safe for the appropriate use of that drug under an appropriate circumstance in a specific disease situation?

Mr. GOODRICH. Certainly.

Senator NELSON. Now, then, how do we bring the word "safe" to bear in the circumstance here of the oral contraceptive when: (1) There are alternative methods; (2) when, let us say, you are dealing with an intelligent, healthy, well-motivated prospective user? How does the word "safe" apply in that respect?

The person has available medical care and a good hospital, has a good physician, has all of the facilities of the medical profession available as contrasted with the situation in which the patient has diabetes, or the patient has a history of high blood pressure, or carcinoma in the immediate family, something like that. How do you evaluate that specific case, the healthy patient with the finest medical facilities available with respect to the phrase "safe within the intent of the law"?

Mr. GOODRICH. As you pointed out, that individual evaluation is for the prescriber, but as I approach it, as I see the responsibility of the Food and Drug Administration, it is to make sure that that prescriber has before him the information that is necessary for the safe, effective use of this drug.

Now, the drugs are essentially very effective. They have two classes of side effects, some troublesome, but not serious; some serious. Our role is to make sure that the material going from the sponsors of these drugs to the prescribers fully discloses both the benefits and the risk and that for the doctor to make a judgment there, after he has taken this lady's history,

after he has made the typical examination, the physical examination, and after he has taken into account all of the things that he is warned about, or cautioned about, or precautioned about, or contraindicated about in the labeling, to make the choice that this is a safe medication for this patient and that this is the one most likely to be effective. (6784)

Senator NELSON. If the patient is a healthy, well-motivated user, or prospective user, who could afford the best medical care, you do not have a problem of weighing the risk of a baby being born not in a hospital, but in a very poor circumstance. You are not weighing the question of whether the woman has psychological problems or diabetes, or disease; we are aiming at the problem of the perfectly healthy person.

Then under those circumstances, where there are alternative methods of birth control and we are dealing with the question of safety, is there any obligation by the doctor to disclose to that patient the benefits and side effects of this contraceptive versus those of alternative methods of contraception?

Dr. EDWARDS. I think there is an absolute responsibility of the physician to: (1) Point out the alternative methods of contraception, and the contraindictions to each, and then I think it is a judgmental consideration on the part of both the physician and the patient in arriving at an appropriate choice of contraceptive methods.

But certainly the physician has a primary responsibility, as we see it, in bringing this information on the safety of this particular product to the patient.

Senator NELSON. To the patient's attention?

Dr. EDWARDS. Right.

Senator NELSON. Because the situation is quite different if there is no disease problem, when there is no other problem.

Dr. EDWARDS. Absolutely.

Senator NELSON. The patient is entitled then to know the facts on thromboembolism or other risks, with a right then to

decide, along with the doctor, whether she would use an oral contraceptive or another device; is that right?

Dr. EDWARDS. Absolutely. And I would again emphasize that in our judgment this is a potent, powerful drug that has to be utilized under the supervision of a competent physician.

Senator NELSON. Then does not the Newsweek poll raise quite a dramatic problem nationwide, when it is your position as well as the position of the former Commissioner Dr. Ley, as well as many witnesses before the committee, that there should be disclosure to the user? Are we not confronted with a very serious situation when the Newsweek poll says that two-thirds of the women interviewed said they were told nothing about side effects?

Dr. EDWARDS. I think very definitely, yes. I think that, unfortunately, the subject of the oral contraceptive has become somewhat of an emotional one in the eyes of many women, in the eyes of the public generally.

I think one of the responsibilities of the Food and Drug Administration is to bring the facts to bear so that they are available to the patient. I think that there have been more women taking the pill than perhaps should have been taking the pill.

I am not sure that this number is absolute, but I think it does indicate there is a need to better inform the patient of the potential dangers of the pill and the risks involved. (6785)

Senator NELSON. If, as you and many others state, it is important to share the knowledge of the side effects with the user, what do we do about the fact that according to the Newsweek poll two-thirds of the doctors are telling the patients nothing about side effects?

Dr. EDWARDS. As I am going to suggest in my prepared testimony, Senator Nelson, I think that the Food and Drug Administration has a responsibility to make sure that these individuals taking the oral contraceptives have received this information, and this is what we are going to propose.

This is what we are planning to do immediately, as a matter of fact.

Senator NELSON. Excuse me. You are planning immediately to do what?

Dr. EDWARDS. We are going to publish in the Federal Register a patient information sheet that we are proposing be placed in all containers of oral contraceptives.

Senator NELSON. That are received by the user?

Dr. EDWARDS. By the user, right.

Senator NELSON. Has that ever been done with any other drug?

Mr. GOODRICH. Yes. There have been a few instances in which it was necessary to have the prescribing information with the package.

Senator NELSON. What drugs are they?

Mr. GOODRICH. Well, I think back—

Dr. JENNINGS. I do not think we have ever required it to the extent that is contemplated in this case. However, we have in at least one recent instance gone contrary to the traditional approach of requiring only the information the doctor wants on the dispense package of a prescription drug. In this instance, we required a warning directed to the patient in a certain class of drugs, the isoproterenol aerosol inhalants. The reasons they were somewhat comparable to what we are facing today, in that the drugs were prescribed in such a way that they could be refilled, the prescriptions could be refilled repeatedly, and the patient therefore had more control over the medication than they would with most prescription drugs.

So we did require a warning on the dispensed containers, directed to the patient.

Senator NELSON. What did the warning say?

Dr. JENNINGS. It simply warned against certain hazards here, associated with overdosage, and that if the usual or

desired effect of release of difficult breathing was not obtained, that the physician should be consulted.

That, of course, does not approach in scope what is contemplated with the oral contraceptives.

Senator NELSON. So this is the first time that you will be proposing that there be a user, so to speak, a user package insert that tells the patient something in detail about the drug?

Dr. EDWARDS. Certainly in the detail that we propose this one in, yes.

Senator NELSON. Will that be in all packages dispensed to the user?

Dr. EDWARDS. We visualize it being in all of the oral contraceptive packages, yes. (6786)

Senator NELSON. Well, I certainly want to commend you for moving in that direction. I had thought maybe there was a legal question, and I had had the counsel draft a bill to accomplish the same purpose, which we introduced yesterday, but which your action will make unnecessary.

Is there any legal problem about the authority of the FDA to require a user package insert?

Mr. GOODRICH. Not if a finding is made as to the product here that is necessary for the safe use of the drug. The legal point being raised, I suppose, has to do with the ordinary rule that prescription drugs dispensed to the user do not themselves carry the warning of hazards, but that information is normally directed to the physician himself, and the law requires that the package dispensed contain such warnings as the prescriber requires in his prescription.

In this case, upon a finding that this kind of information cannot be safely left to word of mouth, that it must be communicated in a more orderly way, this is a safety factor that enters into the new drug decision and can be required, in my opinion.

Senator NELSON. We missed that aspect of the law. I had assumed that it would take some additional legislation, but I am pleased to hear that it does not.

Pardon me for interrupting, Doctor. I had another question I might as well ask right now, because it comes within the next sentence of your prepared statement.

In reading your sentence below, the one we just discussed, "Women whose history and present medical condition include thromboembolic disorders, impaired liver function," as you were reading it, you inserted a "family history of diabetes." This is not in my text.

Dr. EDWARDS. No, I inserted it.

Senator NELSON. So it would read "impaired liver function, family history of diabetes"?

Dr. EDWARDS. Strong family history of diabetes.

Senator NELSON. "Known or suspected cancer of the breast."

This is the question we discussed yesterday with Dr. Cutler, in which he would use, I guess, about the same language you would as to diabetes. We asked him this question, whether the package insert which I believe uses the language "known or suspected cancer of the breast," whether that was adequate. He feels, if I recollect his testimony correctly, that it ought to say about what you said, about diabetes, but that if, as he put it, a sister, mother, or an aunt had cancer of the breast, it should be a contraindication.

Would you agree with that?

Dr. EDWARDS. No, I would not. I would not be quite that forceful in my statement. I think certainly there is an area that we have to keep a very careful eye on, but at this point in time I do not think that our information, our data, would substantiate a statement of that magnitude.

Senator NELSON. So you would not be inclined to even use the words "family history," as you do with diabetes?

Dr. EDWARDS. Not at this point in time. Again, this is one of those areas I think we have to watch very, very carefully, and very shortly we might have to add that.

(6787)

Senator DOLE. Mr. Chairman, we had a subsequent witness yesterday afternoon, Dr. Peterson, who is chairman of the Department of Obstetrics and Gynecology at the Washington Hospital Center, who had much the same indication, that he would not include the family history.

I might also say, Mr. Chairman, that later on in the statement we will be apprised fully of the knowledge of the leaflet that will become the insert. Is that correct?

Dr. EDWARDS. That is correct, yes.

Senator NELSON. Please proceed, Doctor.

Dr. EDWARDS. Thank you.

The risk of having thromboembolic disorders is four to nine times greater for users than for nonusers. Perhaps more accurately state, the mortality for users — I emphasize mortality — is approximately three women per hundred thousand versus 0.5 per hundred thousand in the nonusers. Consequently a few apparently healthy women taking this drug will be affected. For all women, an understanding of this risk and other less-serious adverse reactions will reduce the possibility of serious consequences.

In fact, I must say that the question of the safety of all contraceptives which has come out in these hearings can be clarified only through better public education as to what is involved.

I believe only one witness thus far has suggested to the subcommittee that oral contraceptives be taken off the market. What has been suggested, I think, is that the question of safety is directly related to understanding of risk. I certainly agree and I am prepared today to suggest how we can help the physician better inform his patients on the safe use of oral contraceptives.

First I would like to review the history of the Food and Drug Administration's action with respect to oral contraceptives.

The first oral contraceptive, a combination of mestranol and norethynodrel, was approved for sale in this country in June of 1960. During the next few years the Food and Drug Administration received increasing reports that this oral contraceptive was associated with certain thromboembolic phenomena. A committee of experts was formed by FDA to review and analyze available data and to determine if use of this oral contraceptive resulted in an increase in the incidence of thromboembolic conditions. The committee chaired by Dr. Irving S. Wright, reported in September 1963, that in their opinion no significant increases in the risk of thromboembolic disease had been demonstrated.

Less than 2 years later, in April 1965, the first two sequential products were approved. These new products stimulated wider interest in birth control through use of oral contraceptives.

It was estimated that during 1965 the average number of users of all marketed oral contraceptives in the United States had reached 5 million.

Although the Wright committee found no demonstrated increased risk, the Food and Drug Administration continued its surveillance of adverse reactions. An FDA Advisory Committee on Obstetrics and Gynecology was established under the chairmanship of Dr. Hellman. This committee was asked to consider all of the available evidence and to provide the Food and Drug Administration with the best possible advice. (6788)

This committee of experts issued their first report in August of 1966. They found no adequate scientific evidence at the time to say that these compounds were unsafe for human use. However, the committee noted their concern for better data and made several recommendations which were subsequently acted upon by the Food and Drug Administration.

Included among these were the following:

First of all, the funding of a retrospective study to determine the possible relationship of oral contraceptives to thromboembolic disease.

Second, to support prospective studies utilizing groups of subjects especially amenable to long-term follow-up.

Third, the continuation and strengthening of FDA surveillance system.

Fourth, review of the mechanism for storage, retrieval and analysis of oral contraceptive surveillance data.

Fifth, to support laboratory investigation on carbohydrate metabolism, lipid metabolism, renal function, blood coagulation mechanisms, and potential carcinogenic effects in animals and man.

Sixth, to establish uniform labeling of contraceptive drugs.

Seventh, discontinuation of time limitation for administration of contraceptive drugs.

Lastly, to expedite approval of low dosage oral contraceptives.

The retrospective study was initiated; uniform labeling was achieved; the 2-year limitation was dropped; computer improvements were made in the storage, retrieval, and analysis of surveilance data; better reporting was discussed with the manufacturers; and effects were made to obtain better reporting from hospitals and from prescribers.

By 1966 competition in the oral contraceptive market had resulted in exaggerated and misleading claims. Advertising to physicians and some promotion materials attempted to establish ideas of product superiority which in our judgment had no scientific basis.

As a result, the Food and Drug Administration's efforts to correct this situation led us to the uniform label approach for oral contraceptives.

By early 1968, the improved surveillance system was reporting increasing numbers of thromboembolic diseases associated with women taking the oral contraceptive. At about the same time results of epidemeological studies in Great Britain became available. For the first time these studies demonstrated an increased incidence of thromboembolic disease in users of oral contraceptives. The British data, compiled by Dr. Inman, Dr. Vessey, and Dr. Doll, were reviewed by our experts who also considered the available U.S. data. These experts concluded that there was "a definite association between the use of oral contraceptives and the incidence of thromboembolic disorders."

Based on this conclusion, in June of 1968, FDA sent a letter to all physicians advising them of the British findings.

Senator NELSON. How many cases of thromboembolic disorders had been reported to the department by the end of 1969? Do you happen to have that information? (6789)

Dr. EDWARDS. I would like to refer that question to Dr. Jennings, or a member of his staff.

Senator NELSON. On both deaths and morbidity.

Dr. JENNINGS. We have been compiling these on an annual basis for the past couple of years, and as of December 31, 1969, the total number of reported reactions for that period, July 1, to December 31, 1969, included 15 deaths and 28 nonfatal thromboembolic cases.

Senator NELSON. Over what period of time?

Dr. EDWARDS. From July to December. Is that not correct?

Dr. JENNINGS. That is right. That was for that particular year.

Senator NELSON. How many deaths?

Dr. EDWARDS. Fifteen.

Senator NELSON. And what was the other, thromboembolic?

Dr. JENNINGS. Yes, nonfatal thromboembolic, 28, with about six other miscellaneous adverse reactions.

Mr. DUFFY. Doctor, so I can understand these figures now, are these figures that are actually documented? In other words, it is clear that these are pill-related or are these just incidents which have occurred in people who have used the pill? You may or may not know.

Dr. JENNINGS. Deaths and the nonfatal. In fact, all of these adverse reactions are ones that we attribute to the use of the drug.

Mr. DUFFY. I would assume, then, that if you just looked at the gross number of deaths from thromboembolic accidents of women using the pill, there would be a larger number than 15?

Dr. JENNINGS. Yes, I am sure there would.

Mr. DUFFY. And you narrowed this down to instances where you could be sure it was pill-related?

Dr. JENNINGS. In attempting to establish a cause and effect relationship in any adverse reaction to a drug, where the adverse reaction is one that occurs for other reasons, but the linking of the two is extremely difficult. I think that we cannot always say with absolute certainty that a cause and effect relationship exists.

Now, therefore, even in our labeling, the retrospective studies, for instance, that were done, can establish only that; that they do not establish the precise cause and effect relationship.

We have here the tabulation that we do on these, and although I do not have handy the figure that I think the Senator was asking for, the total that we have to date, we can tabulate this fairly rapidly for you, if you want us to do that.

Senator NELSON. Do you want to submit it for the record?

Dr. JENNINGS. Yes, sir.[1]

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[1] See p. 682

Senator NELSON. I was getting at another aspect of this. We have had witnesses over the past 3 years, distinguished physicians, who deplored the state of reporting on various diseases as being wholly inadequate. By coincidence, last week we had an internist before the committee, who talked about the forms he had to fill out and that he used to religiously report but never got any playback from FDA — this was several years ago — and finally he stopped reporting entirely. (6790

I would like to ask your view about the status of reporting to the FDA on side effects, which you would like to know about. But first, let me read what Dr. Best said before the committee, about 2 years ago.

This is from a statement of William R. Best, chief, Midwest Research Support Center, Veterans Administration, Edward Hines, Jr. Hospital, Hines, Ill. He said:

> I am not sure how much effect the reporting system would have itself. It would produce a universal reporting system. . .that would have a little more meaning than those I have written about that I related to voluntary reporting.
>
> In other words, we would have a better feel for what the total number of cases are. I think we still would not have the whole picture.
>
> I know that in a recent study in Philadelphia, for example, five of the medical school affiliated hospitals tried to set up their own reporting system to catch all the adverse reactions occuring in all of these hospitals. People being people, the way they are, when they went back to check and see how complete their reporting system was, even though the chief of every service told all of his residents and internes to report every case that came through. I think they reported somewhere in the neighborhood of 5 percent. About 95 percent still did not get reported, even though this was the rule of the particular hospital.

This would seem to have been a case where there was a conscientious, specific effort, and according to Dr. Best, about 5 percent of the side effects were reported.

Do you think in your experience, in your judgment, that figure is anywhere near in the ball park of any kind of voluntary reporting the FDA gets on side effects?

Dr. EDWARDS. I do not think I am in a position to give you an absolute figure. I would say without any hesitation our reporting system is poor. As long as we continue to have a reporting system that is voluntary, as it is right now, where we have very little access to the medical records in both hospitals and in doctors' offices, I think the likelihood of our establishing a really accurate, up to date reporting system is not going to be very encouraging.

I think that we have to move in this direction for all drugs, not just for the oral contraceptives. I think a complete adverse reporting system has to be established in this country eventually, if we are really going to provide the surveillance for these powerful drugs that is necessary.

Senator NELSON. I bring this up just to make the point that if the Philadelphia study and the five hospitals with the chiefs of all the services cooperating produced only a 5-percent reporting result, all of your reports on the incidence of deaths and other side effects from the pill, would have to be multiplied by 20 get an accurate figure.

Dr. EDWARDS. I have some reservation as to whether this is an accurate figure. I would add if I were chief of the service in a major teaching hospital and if I could not get my residents and internes to do better than that, I think that maybe I would look at myself, not my staff.

I think we can do better than that. I think maybe some do better than this, but I think the situation is generally poor throughout the country.

Senator MCINTYRE. Mr. Chairman, you asked the question back there, or called for the figures on the number of reports that FDA had received on thromboembolic disease and deaths (6791)
associated with the pill, and I just want to make sure the answer you gave includes all reports which have been received

by FDA from all sources since these drugs came on the market. And if your answer was not inclusive as far as that is concerned, would you please supply it for the record? Do I make myself clear?

Dr. EDWARDS. Yes, I believe they were, were they not?

Senator JENNINGS. No, they were not, and that is what I pointed out to the Senator and said we would compile the figures I think he wants.

Dr. EDWARDS. I was thinking of something else.

Senator MCINTYRE. We had a feeling the figures you gave in response to the chairman's questions were only partial and I wanted to make sure.

Dr. EDWARDS. The period was from July to December, 1969. We will give you the total compilation of the figures.

Senator MCINTYRE. Thank you very much.

Dr. EDWARDS. Again, referring to the letter that the Food and Drug Administration sent to all physicians in 1968, the letter expressed the Food and Drug Administration's conclusion that a definite association had been established—this is between the oral contraceptive and thromboembolic disease, and called their attention to the revised labeling, and asked for their assistance in monitoring adverse reactions.

In 1969, FDA's OB-GYN committee made another comprehensive review of the oral contraceptive problem.

The second report was published on August 1, 1969. In addition to a comprehensive review of the problem, the report contained the results of a well-defined retrospective study on thromboembolic phenomena by Dr. Philip E. Sartwell of Johns Hopkins. The Sartwell study established the association of increased risk of some thromboembolic disorders, confirming the earlier British studies.

Although the committee had also studied the problems relating to carcinogenesis and metabolic effects, they could not

point to conclusive evidence associating these conditions with the use of oral contraceptives.

The committee concluded that "When these potential hazards and the value of the drugs are balanced, the ratio of benefit to risk is sufficiently high to justify the designation safe within the intent of the legislation."

As in their first report, the committee made a number of recommendations.

First of all, they recommended we investigate the carcinogenic and metabolic effect of oral contraceptives in humans.

They recommended we support development of new methods of contraception.

They recommended we support the National Fertility Survey in 1970 by the National Institute of Health.

They recommended that we improve the present system of reporting adverse reaction by financially supporting the use of centers to report reactions on oral contraceptives and by strengthening the present surveillance system of the Food and Drug Administration. (6792)

Lastly, they recommended that we sponsor an annual conference of scientific writers on contraceptive knowledge and accomplishments.

The FDA's review of the committee report and the Sartwell study led to a decision that a change in the uniform labeling was necessary. Accordingly, on November 14, 1969, we met with industry representatives to discuss the revised uniform labeling which has been required since January 1 of this year.

In December when I became Commissioner, the decision was made to issue a letter to all U.S. physicians, hospital pharmacists, and hospital administrators. In it, I warned that "carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than nonusers" and I strongly urged physicians to familiarize themselves with the revised labeling.

I suggested that "a full disclosure of the potential adverse effects" to patients is advisable, and I also again requested their assistance in reporting adverse reactions to the Food and Drug Administration.

In addition, in December of 1969, reports came to our attention of the British announcement advising practitioners to prescribe only products containing .05 milligrams or less of estrogen. I indicated then that the Food and Drug Administration would await full data from England and evaluate this and our own data before making a decision on whether any action should be taken with regard to the oral contraceptives containing high doses of estrogen.

I would like to say in this regard, we just yesterday or the day before received a message from the British, inviting us to come to London on March 18 with appropriate individuals from the Food and Drug Administration and the National Institute of Health, to review their data.

So this month we will have the British information.

Senator NELSON. You will be sending a delegation shortly, did I understand you to say?

Dr. EDWARDS. That is right. We are to be there on March 18.

Senator NELSON. Are you, as Commissioner, going with the delegation?

Dr. EDWARDS. Yes, sir, I am. Three people from the Food and Drug Administration, in addition to two from the National Institute of Health.

Senator NELSON. If their data satisfies you and the group with you that oral contraceptives with more than 50 micrograms of estrogen do in fact induce a higher incidence of thromboembolism, will it be the decision of the FDA to order from the market all of those in this country that exceed 50 micrograms?

Dr. EDWARDS. Obviously, I think it would depend to a certain degree on the quality, or at least our interpretation of the quality of their data.

I think we have to continually bear in mind the formulation of these products, and this is certainly one of the alternatives that we have to think about if the data warrant it such a decision.

Senator NELSON. That is what I am getting at. If you and your scientists are satisfied with the quality of the research and conclude that they are correct, that over 50 micrograms increases the incidence of thromboembolism, would you be (6793)
inclined then to order from the market all of our oral contraceptives that exceed that?

Dr. EDWARDS. Again, I think we would have to give this very serious consideration. If the data were of the quality that we insist upon in the studies that we currently have ongoing in this country, I think we would have to consider this, yes.

Senator NELSON. Is there any question of the effectiveness of the 50 microgram tablet—I am not talking about the side effects—the effectiveness in preventing pregnancy, inhibiting ovulation?

Dr. EDWARDS. I would like to have Dr. Jennings answer that question, if I may. I think he perhaps is a little more familiar with it.

Dr. JENNINGS. I think that the picture is perhaps not quite as simple as simply a difference between .05 milligrams of estrogen and .08 milligrams. The two commonly used estrogens are ethinyl estradiol, which is usually present in a quantity of .05 milligrams, and mestranol, which is usually present in the higher dosage.

Both of these seem to be effective at those respective levels. There was some indication that a lesser amount of mestranol, the one that is usually present in the higher amount, might not be as effective as manifested by breakthrough bleeding, I believe, and also by pregnancy rates in some of the studies where this amount was lowered.

So I think that in addition to simply considering the two levels of estrogen, a certain difference in the estrogenic strength of the two products, the two compounds, has to be considered.

In addition, the products currently on the market all include progesterones, either to be taken in combination throughout the period of medication, or to be taken in sequence. The progesterones vary also in their estrogenic effect. So that this also has some bearing on the potential for the side effects that might be attributed to estrogenic activity.

I think all of this will have to be taken into consideration when the British data are available to us.

Senator NELSON. Thank you.

Senator MCINTYRE. Mr. Chairman, a question. I would like to know if you have received any of the British data as of now.

Dr. EDWARDS. No.

Senator MCINTYRE. Thank you.

Dr. EDWARDS. I think with all due respect, it is a matter of their not having been able to tabulate their information. I think it has been rather substantial. And I think they have had trouble pulling it all together. It has not been because they have been trying to keep it from us, it is just they wanted to get it in order before we had an opportunity to look at it.

Senator MCINTYRE. Thank you.

Dr. EDWARDS. Another action taken soon after I became Commissioner was to convene a meeting of our OB-GYN Advisory Committee. I met with this group on January 21 to re-evaluate available information on oral contraceptives. I believe the advice and counsel of this group is important to our work in this area, and I intend to meet with them every 30 to 60 days.

I think this is perhaps an appropriate occasion to announce that Dr. Allan C. Barnes, professor and chairman of the Department of Obstetrics and Gynecology at John Hopkins University is the new chairman of our advisory committee, replacing Dr. Hellman. (6794)

Dr. Barnes will chair our meeting next Wednesday when we will review some of our present research projects.

I would like at this time to review some of our studies which are now under way. There are several general areas on which the total scope of the Food and Drug Administration's present program is based.

Information is being sought on the degree and mechanism of changes brought about by the oral contraceptive and the indications of these changes.

Also, we are trying to determine whether certain of these drugs, or their ingredients, have unique pharmacological properties; whether high risk subpopulations can be identified; and to what degree can findings observed in animals be extrapolated to the human population.

Clinical and animal studies presently under way and supported by the Food and Drug Administration include:

A retrospective study of a cost of $175,000 on the relationship between thromboembolic phenomena and oral contraceptive use conducted by Dr. Philip Sartwell at the Johns Hopkins University School of Hygiene and Public Health. Here we are planning to extend this for another year, beginning next month, at a cost of approximately $75,000.

We have an investigation going on of the carcinogenic potential, hematologic, and endocrine effects of two experimental oral contraceptive formulations using dogs and monkeys treated over a prolonged period of time. This continuing study by the International Research and Development Corp., was begun late in 1968 at a cost of $372,000.

We have an intensive study of changes in blood cogulation and fibrinolysis in women using oral contraceptives, which was initiated at the New York University School of Medicine in May 1969, at an annual cost of $27,000. Results are expected early in 1971.

We have the study of the University of Rochester on the possible effects in women of oral contraceptives on renal, bladder and ureteral function and the incidence of infection which was initiated in May 1969, at an annual cost of $77,000.

We have the study at Temple University on the effects of oral contraceptives on lipid metabolism in subhuman primates and women of reproductive age, which was initiated in May of 1968 at an annual cost of $118,000.

We have a prospective study on the effects of prolonged use of oral contraceptives on carbohydrate metabolism in a large group of women, and this has been underway at the University of Miami since June 1967, at annual cost of $63,000.

Lastly, we have a study at Temple University on the effects of oral contraceptives on cervical cytology which was initiated in July of 1969 at a cost of $95,000.

All of these studies are currently costing the Food and Drug Administration $380,000 annually.

Senator DOLE. Dr. Edwards, there has been some testimony that additional funds are needed to research oral contraceptive research. Do you feel additional funds are needed, and if so, in what specific areas? (6795)

Dr. EDWARDS. I think without any hesitation I would say that our research efforts in this whole general field have to be increased, both within the Food and Drug Administration and at the National Institute of Health.

Senator DOLE. You indicated on page 10 an increase of $700,000 to in excess of $3 million.

Dr. EDWARDS. When I say the 3 million, I am talking a ballpark figure and I am talking about total research. Again I do not mean that we are capable of taking this kind of increase all at once, but I think over a period of several years. I think this is the ballpark figure that we are talking about.

Senator DOLE. There are specific areas now with reference to oral contraceptives, where research could be done if you had the money, is that your opinion?

Dr. EDWARDS. I think additional research needs to be done in a number of these areas. This whole area of the carbohydrate metabolism, lipid metabolism, the possible effect or rela-

tionship between the oral contraceptive and carcinogenic effects have to be looked into in much greater depth than we have at this point in time. I am speaking only for the Food and Drug Administration, of course. Our research funds are extremely limited, and we have had to establish priorities. And as I can assure you, in establishing these priorities, the oral contraceptives have been up at the top of our list. So we have spent most of our funds on research in the oral contraceptives.

There are other areas, but I think these are certainly some of the main areas where additional research needs to be done.

Senator DOLE. Thank you

Senator NELSON. May I pursue that subject a little further?

I guess every witness has commented on the question, including General Draper and Dr. Guttmacher, as well as various physicians and specialists who have appeared before the committee. They have all deplored the lack of adequate amounts of research. One of the points raised, I think by Dr. Corfman of NIH, although the record will correct me if it were not he, was that unfortunately there has been no dosage level research done in terms of trying to find out how low a dosage of progesterones and estrogens may be given and still be effective and what reduction in incidence of side effects might occur as a consequence of lower dosages or lower dosages in various combinations.

And you know, of course, that the first pills were 150 micorgrams of estrogen and were effective, and 100 were effective, and 75 were effective. The British seem to think 50 are effective.

Would you consider it an important piece of research to establish some protocol for comprehensive investigation of this aspect of the oral contraceptive?

Dr. EDWARDS. Very definitely. I think this is an area in which far too little has been done. I am thinking in terms of the formulation of these products, the minimum amount that will provide the efficacy that we want.

I think some of this, however, has to also be done by the industry. And who does what is a rather difficult question for me. The answer is a difficult one. But I think without any question this is an area I should have mentioned in greater detail. I think much more has to be done, and I think we have to play an important role in stimulating this research, either we do it or we stimulate industry to do it. (6796)

But I think without any question this is one of the most important areas.

Senator NELSON. Again, this is a legal question: What authority does the FDA have to require drug companies to do additional research after a drug has been placed on the market? In this case dose level studies?

Do you have authority to require such data?

Dr. EDWARDS. I would like to have Mr. Goodrich answer that. I am not sure about our authority, but after all, in approving new drugs, we have to evaluate and judge the adequacy of the clinical investigations that have led up to the marketing of this drug, and in our judgment, if these are not adequate, then I think we certainly can go back to that particular company and say more study needs to be done in these particular areas; but legally, I would like to turn to Mr. Goodrich.

Mr. GOODRICH. Our legal authority is to require the companies to make either a regular or special report. A report could be called for on any phase of the safety decision. If we attempt to require the research, our ultimate administrative step would be to withdraw approval.

We have legal authority to withdraw approval at any time we find that there is a lack of adequate evidence, either of safety or of effectiveness.

So what would have to be done would be to identify with the company those areas in which additional research was needed, some kind of time within which this could be done, and say that if it were not done, they would be risking the loss of the product by the withdrawal of approval.

We do not have any direct authority to say do this research, but the ultimate withdrawal possibility does facilitate a good deal of research.

Senator NELSON. In the specific case at hand, or with any drug, a potent one, anyway, extensive use over a period of years develops information that could not have been developed by FDA, so you have a case here where where thromboembolism was proven quite early, and statistics have accumulated to support it.

Do you have the authority to say it is pretty clear that a drug could be developed with less dramatic side effects, a lower incidence, therefore you must proceed with some protocol for investigating this possibility?

Mr. GOODRICH. We think so. But as I say, our ultimate, if they refuse to do it, our ultimate step would have to be to withdraw approval.

Senator NELSON. I understand.

I would like to ask another question in the research field. This concerns the report based on the workshop sponsored by NIH on "Metabolic Effects of Gonadal Hormone and Contraceptive Steroids." In the preface on page 9, I quote: (6797)

> Until recently, the metabolic effects of the contraceptive steroids have been inadequately investigated or ignored. These accumulated data and other suggest that no tissue or organ system is * * * a biological function and/or more * * * effect of contraceptive steroids. Many of these changes appear to be reversible after short periods of treatment. But it is impossible to form judgments on the reversibility of some of the changes resulting from prolonged administration. This question becomes more important daily for the many patients who already had long-term contraceptive steriod treatment.

It seems to me this raises a very serious question, since we really do not know what the consequences of these metabolic changes are over a long period of time.

My question is: Are you satisfied that we are doing enough research on this aspect of the problem, and if not, do you have some view about what we ought to be doing?

Dr. EDWARDS. By "this aspect of the problem," you are referring to the time period over which the oral contraceptive is given a particular patient; right?

Senator NELSON. And the metabolic effects of it.

Dr. EDWARDS. And the permanent effects this might have on the patient's metabolic system, et cetera.

I share with you concern about this, and certainly I think this is an area that we have to look at very seriously, along with groups at the National Institute. I have personal reservations about allowing the oral contraceptive to be given over indefinite periods of time. I have no knowledge of scientific evidence at the moment that would substantiate this view, but I think that some of the retrospective and prospective studies we are proposing or actually have in progress at the moment will help answer some of these questions. But it is a very serious subject of concern and I think it is one I hope our advisory group will address themselves to this next week.

Senator NELSON. That is the question of extended administration without interruption?

Dr. EDWARDS. Right, and what kind of studies would best allow us to make some scientific judgment on the advisability of this, or what is the ideal length of time over which one of the oral contraceptives can be given.

Senator NELSON. As you know, we have had a number of witnesses who have expressed their opinion, again without having the proof, as you said, who had reservations such as you have indicated you have.

One of the witnesses said that he would not want to have it used more than 2 or 3 years continuously without interruption.

Others expressed a similar viewpoint about long-term usage, simply because we do not have the studies that would

indicate whether or not the metabolic changes that are effectuated on account of the administration of the pill have any long-term damaging effects.

Do I understand you to say that the new committee being constituted now on obstetrics and gynecology will address itself to the question of length of time the drug should be administered?

Dr. EDWARDS. I think there are a number of areas that we would like to have them address their attention to, but this certainly is one of the areas that should receive a high priority on the agenda of the committee. (6798)

To complete the review of our studies in which we are indirectly involved, I will mention that we have participated in the monitoring of the prospective study of oral contraceptive users being conducted under support from the National Institute of Child Health and Development at the Kaiser Permanente Foundation in Walnut Creek, Calif.

In addition, we have participated in the review of two planned retrospective studies relating to the possible effects of oral contraceptives on carcinoma of the breast submitted to and approved by the National Institute of Child Health and Development. Funding for these studies has not yet been approved.

This investment in research, in our judgment, is necessary to better define the hazards of the oral contraceptive.

The questions of safety must be answered in so far as is possible for science to find the answers. And we at the Food and Drug Administration must continuously review our previous decisions in light of new scientific knowledge.

We have plans underway to develop other studies. These include the effect of oral contraceptive drugs in prediabetic and diabetic patients: cytogenetic studies in spontaneous and induced abortions; development of other techniques to assess the effects of oral contraceptives on endocrine function during adolescence; and the metabolism of the hormonal contraceptives and possible interaction with other drugs.

In order to get these studies under way, it will require an increase in our current research budget from approximately $700,000 in fiscal year 1970, to over $3 million.

I would like to turn to another subject which will require very substantial funding if we are to do an effective job. This is the need for a comprehensive drug surveillance system.

Because of the limited nature of premarketing clinical trials, we cannot expect to observe all of the adverse reactions that may occur. We are dealing with comparatively small numbers of patients who are screened carefully and regularly. The difficulty of detecting adverse reactions is great. Our statisticians tell us that an adverse reaction expected to occur at a rate of 1 in every 1,000 will not be observed at all in 37 percent of studies using 1,000 subjects. In other words, to be 97 percent certain of observing such a high rate of adverse reaction, a study would need to include 10,000 or more subjects.

Therefore, it is essential that all approved drugs be kept under close surveillance through an effective adverse reaction reporting system. At present this system in the United States depends for the most part on voluntary submission of adverse reactions by physicians and hospitals and, of course, the required reports from the drug manufacturers. It is unfortunate, but true, that we receive reports on only a small percentage of the total number of adverse reactions that occur. This limited access to the medical record makes it extremely difficult to evaluate cause and effect. We must move in the direction of significantly improving our surveillance system. I would estimate it would take at least a third of our present budget to establish such a comprehensive reporting system.

Senator NELSON. Would this be compulsory? (6799)

Dr. EDWARDS. No. At least we are not in any position at this point to make reporting compulsory. But I think with the right kind of a system, a computerized system, where the medical record is far more computerized than it is at the present time would be helpful. I do not think it would have to be a compulso-

ry system to get a reasonably good response in terms of drug reporting.

Senator NELSON. We had that, of course, in some of the communicable diseases.

Dr. EDWARDS. I think though that for this, Senator Nelson, for this to be effective, really an effective reporting system, we are eventually going to have to get the record out of the doctor's office. Obviously this is where some of the minor reactions occur and it is not just the hospital record.

I think the time is coming when we will have a medical record that is automated, a centralized medical record, if you will. When this happens, I do not believe it will be a matter of whether reporting will be compulsory or noncompulsory, it will be on the record.

And I think all of this is within the realm of possibility.

Senator NELSON. I must say, in looking at one of the reports submitted to the physician by the FDA, the number of questions and the fine lines, that it is a kind of discouraging thing for the physician to fill out. As you know, all Federal forms somehow or another get to be enormously detailed. It might help, I suppose, if there were some way to simplify it.

Dr. EDWARDS. I suspect you are correct, and I have not had an opportunity to look at the system that we use, but I am certain that what you say is true.

And I think in terms of developing an adverse reporting system, we have to look at what the FDA requires, as well as what the system provides generally. So we will be looking at out capabilities in this regard, too.

Senator NELSON. Thank you.

Dr. EDWARDS. Under the present system we try to keep the physician abreast of adverse reactions as we become award of them. This is certainly true with regard to the oral contraceptives. There is no question that it is vitally important to communicate this information to the physician, but there is also

corresponding need to keep the patient well informed. I believe that the patient should receive as much accurate information as is necessary for her to make certain decisions.

Let me examine for just a moment how women are currently being informed as regards the oral contraceptive.

They get a good deal of information and misinformation from sources other than the physician—through newspapers, pamphlets, books, television, and from discussion with others. This additional information is reaching a large number of people in a short period of time. While we can control the prescribing information which goes to the physician and any printed or graphic matter that may ultimately reach the patient through him, we have no such opportunity to see that other presentations are accurate, balanced, and properly informative. (6800)

I have come to the conclusion that the information being supplied to the patient in the case of the oral contraceptive is insufficient and that a reevaluation of our present policies is in order.

Accordingly, I have asked our Bureau of Drugs to examine this area of consumer information and to give me their recommendations.

I have with me today, which I will submit to you, a statement which we are going to publish in the Federal Register so that all interested parties will have an opportunity to comment on it. This statement is the proposed language for a reminder leaflet of uniform content which will be placed by the manufacturer into each package of oral contraceptives produced.

This leaflet is designed to reinforce the information provided the patient by her physician. I emphasize the word "reminder" as its purpose is to recall to the patient her discussion with the physician when she made her decision to begin taking an oral contraceptive.

I will not read this unless you would like.

(The statement follows:)

WHAT YOU SHOULD KNOW ABOUT BIRTH CONTROL PILLS

(ORAL CONTRACEPTIVE PRODUCTS)

All of the oral contraceptive pills are highly effective for preventing pregnancy, when taken according to the approved directions. Your doctor has taken your medical history and has given you a careful physical examination. He has discussed with you the risks of oral contraceptives, and has decided that you can take this drug safely.

This leaflet is your reminder of what your doctor has told you. Keep it handy and talk to him if you think you are experiencing any of the conditions you find described.

A WARNING ABOUT "BLOOD CLOTS"

There is a definite association between blood-clotting disorders and the use of oral contraceptives. The risk of this complication is six times higher for users than for non-users. The majority of blood-clotting disorders are not fatal. The estimated death rate from blood-clotting in women *not* taking the pill is one in 200,000 each year; for users, the death rate is about six in 200,000. Women who have or who have had blood clots in the legs, lung, or brain should not take this drug. You should stop taking it and call your doctor immediately if you develop severe leg or chest pain, if you cough up blood, if you experience sudden and severe headaches, or if you cannot see clearly.

WHO SHOULD NOT TAKE BIRTH CONTROL PILLS

Besides women who have or who have had blood clots, other women who should not use oral contraceptives are those who have serious liver disease, cancer of the breast or certain other cancers, and vaginal bleeding of unknown cause.

SPECIAL PROBLEMS

If you have heart or kidney disease, asthma, high blood pressure, diabetes, epilepsy, fibroids of the uterus, migraine

headaches, or if you have had any problems with mental depression, your doctor has indicated you need special supervision while taking oral contraceptives. Even if you don't have special problems, he will want to see you regularly to check your blood pressure, examine your breasts, and make certain other tests.

When you take the pill as directed, you should have your period each month. If you miss a period, and if you are sure you have been taking the pill as directed, continue your schedule. If you have not been taking the pill as directed and if you miss one period, stop taking it and call your doctor. If you miss two periods, see your doctor even though you have been taking the pill as directed. When you stop taking the pill, your periods may be irregular for some time. During this time you may have trouble becoming pregnant. (6801)

If you have had a baby which you are breast feeding, you should know that if you start taking the pill its hormones are in your milk. The pill may also cause a disease in your milk flow. After you have had a baby, check with your doctor before starting to take oral contraceptives again.

WHAT TO EXPECT

Oral contraceptives normally produce certain reactions which are more frequent the first few weeks after you start taking them. You may notice unexpected bleeding or spotting and experience changes in your period. Your breasts may feel tender, look larger, and discharge slightly. Some women gain weight while others lose it. You may also have episodes of nausea and vomiting. You may notice a darkening of the skin in certain areas.

OTHER REACTIONS TO ORAL CONTRACEPTIVES

In addition to blood clots, other reactions produced by the pill may be serious. These include mental depression, swelling, skin rash, jaundice or yellow pigment in your eyes, increase in blood pressure, and increase in the sugar content of your blood similar to that seen in diabetes.

POSSIBLE REACTIONS

Women taking the pill have reported headaches, nervousness, dizziness, fatigue, and backache. Changes in appetite and sex drive, pain when urinating, growth of more body hair, loss of scalp hair, and nervousness and irritability before the period also have been reported. These reactions may or may not be directly related to the pill.

NOTE ABOUT CANCER

Scientists know the hormones in the pill (estrogen and progestrone) have caused cancer in animals, but they have no proof that the pill causes cancer in humans. Because your doctor knows this, he will want to examine you regularly.

REMEMBER

While you are taking ____, call your doctor promptly if you notice any unusual change in your health. Have regular checkups and your doctor's approval for a new prescription.

Senator NELSON. I would appreciate it if you would read it. I have not read it yet. I might have a question.

Dr. EDWARDS. I might read the first page and then summarize the rest of it and any of the technical matter. The title of this is "What You Should Know About Birth Control Pills."

> All of the oral contraceptive pills are highly effective for preventing pregnancy, when taken according to the approved directions. Your doctor has taken your medical history and has given you the risks of oral contraceptives, and has decided that you can take this drug safely.
>
> This leaflet is your reminder of what your doctor has told you. Keep it handy and talk to him if you think you are experiencing any of the conditions you find described.

Then the next section is a warning about blood clots. Here we indicate there is a definite association between bloodclotting disorders and the use of oral contraceptives. The risk of this

complication is six times higher for users than for nonusers. And although the majority of blood-clotting disorders are not fatal, the estimated death rate from blood clotting in women not taking the pill is 1 in 200,000 each year. For the user, the death rate is about 6 in 200,000. (6802)

Women who have blood clots in the legs, lungs or brain, should not take this drug. You should stop taking it and call your doctor immediately if you develop severe leg or chest pain, if you cough up blood, if you experience sudden or severe headaches, or if you cannot see clearly.

Senator NELSON. The figures that have been used frequently before the committee indicate that hospitalization from blood clotting occurs in 1 of every 2,000 users. Is there any reason for not using that figure in here?

Dr. JENNINGS. I think, Senator, there are any number of ways we could express this. All the data we have on this particular phenomenon, both morbidity and mortality, are somewhat inexact. I think what we attempted to do here was zero in on the most serious aspect of this, and to give the woman some idea of the magnitude of the problem.

In other words, it would not be enough for her to know that the rate was increased for users by a certain number, four to nine times, unless she had some idea of magnitude; one in a thousand multiplied by four to nine times would be a large number.

One in 200,000 multiplied approximately six or four to nine would be a much smaller number. And I think that is what we are trying to get across here, that there is an increased risk among users compared to nonusers and that for the most serious result of this complication, the fatality, occurs in this order of frequency.

Senator NELSON. I notice that in the Dear Doctor letter of June 28, 1968, which included the package insert, the hospitalization rates of morbidity age 20 to 24, it is 47 per 100,000. If I interpret this correctly, you have the hospitalization rate of almost one in 2,000. Am I interpreting it correctly?

Dr. JENNINGS. Yes, I think that would be one way of putting it. That was ahospitalization rate, which is one indication of morbidity. I think what we attempted to do here was not a literal translation of the information given to the physician, who is, after all, much more sophisticated and capable of handling these numbers, but to try in a simple fashion to alert the woman to the fact that there was an increased risk and then to give her some idea of the magnitude of this, especially in relation to the most important, that is, the fatality.

Senator NELSON. Well, all I say, as just a layman reading it, is that when you talk about the death rate being one in 200,000 for women not taking the pill and for users six in 200,000, those are very large figures. But when you get down to the more practical aspect in a higher incidence and talk about almost one in 2,000 being hospitalized, which is a very high incidence, it is a figure that is much easier to understand, and does not just talk about deaths, it talks about hospitalization rates.

I just raise the question because it seems to me, a very significant statistic to include. If I were a patient, I would want to know that one in 200,000 die who were not taking the pill and six in 200,000 do who are taking it, and I might say to myself, well, that six out of 200,000 is very low.

On the other hand, if you would say one out of 2,000 is going to be hospitalized by blood clots alone, that is a pretty dramatic (6803)
figure, and I would think it is one that is quite understandable and ought to be used.

Dr. EDWARDS. I think your point is well taken, and I would emphasize that this is not the final package. This is for discussion purposes primarily, and we certainly anticipate making changes, as requested by groups such as your committee and others.

I think your particular point is a good one.

Senator DOLE. Dr. Edwards, this insert has been in the making for sometime; is that correct?

DR. EDWARDS. Right.

Senator DOLE. I am not certain whether the average person realizes there is any great risk if it is one out of 200,000 or six out of 200,000. We have had witnesses indicate we should not include a laundry list with medication, because to do so would confuse the patient.

I am not certain where you draw the line, whether you should indicate any numbers, whether you should indicate there is some risk. The question is how to best communicate with patients, but we do not want to frighten the few people left who are not frightened as a result of these hearings.

I would hope that we do not try to rewrite the memorandum in committee hearing.

Senator NELSON. I hope the Commissioner did not think I was trying to rewrite the memorandum; I was just asking the question for information purposes because I thought it was a good question. I would not think of trying to write the memorandum, but I would think it is within the province of a member of the committee or any citizen in America, and there are 200 million of them, to ask a question.

Senator DOLE. We have asked several questions.

Dr. EDWARDS. Certainly our intent is not to frighten anyone away from the pill, but it is our intent to prepare a document, and as I say, I will not stand on this particular document, but prepare a document that gives the facts in an unemotional way so that the many, many patients in this country who are receiving the oral contraceptive by renewal of prescriptions, et cetera, will at least have some access to appropriate information.

Senator DOLE. Will this be an additional piece of information, in addition to what the drugmaker himself may include? Are we going to have two pieces of literature to read, or does this supersede anything else?

Dr. EDWARDS. I believe I am correct—Dr. Jennings can correct me—that at the present time there are no inserts in these packages per se, are there?

Dr. JENNINGS. No, there are not.

Dr. EDWARDS. Except for the physician.

Dr. JENNINGS. That is right. But I think the Senator is referring to the booklets that are frequently prepared.

Senator DOLE. Right.

Dr. JENNINGS. For patient use.

Senator DOLE. You have one entitled "So Close to Nature" which we had last week.

APPENDIX C

FDA's "Dear Doctor" Letter Of June 28, 1968, And Revised Uniform Labeling For Oral Contraceptives

APPENDIX C

DEPARTMENT OF HEA' TH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,

Washington, D.C., June 28, 1968.

DEAR DOCTOR: Since 1960, when the first oral contraceptive was marketed in the United States, these drugs have been prescribed in a volume which may exceed that of any other potent medication. According to current estimates, more than six million American women now use oral contraceptives. As the drugs have been used more widely, adverse reactions, not known at the time of original Food and Drug Administration approval, have become evident; the labeling of the drugs has been revised from time to time to include this new knowledge.

The most recent data developed in studies conducted in Great Britain confirms what had been suspected: *there is a definite association between the use of oral contraceptives and the incidence of thromboembolic disorders.* New labeling, which will be in use by July 1, 1968, contains excerpts from the British reports and appropriate revisions of prescribing information. The labeling is uniform for all drugs in this class, and is in the standard format recommended by the FDA for all drug labeling.

A copy of the revised uniform labeling is attached. We urge you to give careful consideration to the information under the various cautionary headings in the labeling.

We ask, too, for your assistance in monitoring adverse reactions by reporting all such reactions to the Food and Drug Administration. A supply of the standard reporting form (FD 1639), shown in facsimile on the reverse of this letter, may be obtained by writing to: Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

Attachment:

Revised uniform labeling

Uniform Section of Oral Contraceptive Labeling

Chemistry

This should include generic name, amount, chemical name and the structural formula of each active ingredient.

Mechanism of Action

(As presented in current package insert.)

Indications

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

Contraindications

1. Patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or with a past history of these conditions.

2. Patients with markedly impaired liver function.

3. Patients with known or suspected carcinoma of the breast.

4. Patients with known or suspected estrogen dependent neoplasia.

5. Undiagnosed abnormal genital bleeding.

Warnings

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Studies conducted in Great Britain and reported in April 1968 [1,2] estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

COMPARISON OF MORTALITY AND HOSPITALIZATION RATES DUE TO THROMBOEMBOLIC DISEASE IN USERS AND NON-USERS OF ORAL CONTRACEPTIVES IN BRITAIN

Category	Mortality Rates		Hospitalization rates (morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of oral contraceptives	1.5/100,000	3.9/100,000	47/100,000
Nonusers	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out

[1] Inman, W.H.W. and M. P. Vessey, British Medical Journal 2:193-199, 1968.

[2] Vessey, M. P. and R. Doll, British Medical Journal, 2:199-205, 1968.

before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. There, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginum, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal,hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The

mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

9. Because of the effects of estrogens on epiphyseal closure * * * should be used judiciously in young patients in whom bone growth is not complete.

10. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.

11. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis	Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Cerebrovascular accidents	Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives (Consult the clinical section.)

Nausea	Change in weight (increase or decrease)
Vomiting	Changes in cervical erosion and cervical secretions

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea during and after treatment
- Edema
- Chloasma or melasma
- Breast changes: tenderness, enlargement and secretion
- Suppression of lactation when given immediately post-partum
- Chloestatic Jaundice
- Migraine
- Rash (Allergic)
- Rise in blood pressure in susceptible individuals
- Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

- Anovulation post treatment
- Prementrual-like syndrome
- Changes in libido
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Fatigue
- Backache
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Itching

The following laboratory results may be altered by the use of oral contraceptives (see sections on clinical laboratory):

- Hepatic functions: Increased sulfobromophthalein and other tests
- Coagulation tests: increase in prothrombin Factors VII, VIII, IX and X
- Thyroid functions: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 values
- Metryapone test
- Pregnanediol determination

Animal Studies

This should include results of acute, chronic toxicity and reproduction studies using the compounds present in the product. Significant laboratory and pathologic findings should be mentioned.

Endocrine and metabolic screening. State results on dose per weight basis.

Clinical Data

Efficacy—This should include the number of cycles completed. Breakdown by number of patients completing a specific number of cycles should also be mentioned. State number of pregnancies in number per 100 woman years. Pearl's formula or life table technique should be used. The following statement is permitted if applicable: "Virtually 100% effective when used according to directions."

Adverse Reactions Clinical Laboratory Results—This should include liver, thyroid, renal functions, coagulation tests, endocrine function as well as routine hematology and cytology.

Dosage And Administration

This should include routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

Availability

Bibliography

Reference, not a complete bibliography.

May 10, 1968 / Food and Drug Administration / U.S. Department of Health, Education, and Welfare / Washington, D.C. 20204.

APPENDIX D

FDA's "Dear Doctor" Letter Of January 12, 1970, And Revised Uniform Labeling For Oral Contraceptives

APPENDIX D

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,

Washington, D.C., January 12, 1970.

DEAR DOCTOR: I am enclosing revised labeling for oral contraceptives to reflect the latest findings on safety and efficacy, as reported by the Obstetrics and Gynecology Advisory Committee in August 1969. An American study confirms previously reported studies in Great Britain which show a relationship between the use of oral contraceptives and the occurrence of certain thromboembolic diseases. These carefully designed retrospective studies show that users of oral contraceptives are more likely to have thrombophlebitis and pulmonary embolism than non-users. Studies in Great Britain also show increased risk of cerebral thrombosis and embolism in users of oral contraceptives. A British study found a hospitalization rate (an index of morbidity) in women age 20-44 to be 47 per 100,000 in users compared to five per 100,000 in non-users.

The American study, although not designed to evaluate differences between products, also suggests there may be an increased risk of thromboembolic disease in users of sequential products. This difference in risk cannot be quantitated, and further studies are needed to confirm the observation.

The British Committee on Safety of Drugs recently advised practitioners in that country that only products containing 0.05 mg. or less of estrogen should normally be prescribed because reports of suspected adverse reactions indicated there is a higher incidence of thromboembolic disorders with products containing 0.075 mg. or more of estrogen than with products containing the smaller dose. This finding has not been confirmed by other studies.

The FDA is planning studies that will determine, among other things, the thromboembolic effect of various products. You will be kept informed as results become available.

Other aspects being investigated in separate studies underway or pending are cervical cytology, carbohydrate metabolism, serum lipids, urinary tract function, blood coagulation, effects on endocrine function in adolescents, breast pathology, outcome of pregnancy, and cytogenetic effects.

In the United States during 1969 an estimated 8.5 million women took oral contraceptives monthly. The unsurpassed clinical efficacy of these products is well established. Although reported pregnancy rates vary from product to product, the effectiveness of sequential products appears to be somewhat lower than that of the combination products.

I strongly urge you to familiarize yourself with the labeling, particularly with the cautionary material contained in the sections headed Contraindications, Warnings, Precautions, and Adverse Reactions. As the prescribing physician, you are in the best position to determine the extent of your discussion of this material with your patient. In most cases, a full disclosure of the potential adverse effects of these products would seem advisable, thus permitting the participation of the patient in the assessment of the risk associated with this method.

I also request your assistance in continuing our assessment of the safety of oral contraceptives. Your reports of adverse reactions will help us to do this. A supply of the standard reporting form (FD 1639), shown in facsimile below, may be obtained from the Bureau of Medicine, Food and Drug Administration, Washington, D.C. 20204.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Acting Commissioner of Food and Drugs.

Attachment:
Revised labeling

Oral Contraceptive Labeling

Description

This section includes generic name, amount, chemical name and the structural formula of each active ingredient.

Actions

Combination oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression. Changes in cervical mucus and endometrium may be contributory mechanisms.

Sequential oral contraceptives: The mechanism of action is inhibition of ovulation resulting from gonadotropin suppression.

Special Note

Oral contraceptives have been marketed in the United States since 1960. Reported pregnancy rates vary from product to product. The effectiveness of the sequential products appears to be somewhat lower than that of the combination products. Both types provide almost completely effective contraception.

An increased risk of thromboembolic disease associated with the use of hormonal contraceptives has now been shown in studies conducted in both Great Britain and the United States. Other risks, such as those of elevated blood pressure, liver disease and reduced tolerance to carbohydrates, have not been quantitated with precision. Long term administration of both natural and synthetic estrogens in subprimate animal species in multiples of the human dose increases the frequency for some animal carcinomas. These data cannot be transposed directly to man. The possible carcinogenicity due to the estrogens can neither be affirmed nor refuted at this time. Close clinical surveillance of all women taking oral contraceptives must be continued.

INDICATIONS

The Obstetrics and Gynecology Advisory Committee considered the following indications acceptable: contraception, endometriosis, and hypermenorrhea. These indications may be used in the labeling when efficacy has been demonstrated in each case. Any other claims will be evaluated on the basis of efficacy data available to support each.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.
2. Markedly impaired liver function.
3. Known or suspected carcinoma of the breast.
4. Known or suspected estrogen dependent neoplasia.
5. Undiagnosed abnormal genital bleeding.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary emoblism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis and pulmonary embolism and the use of oral contraceptives. There have been three principal studies in Britain[1-3] leading to this conclusion, and one[4] in this country.

---

[1] Royal College of General Practitioners: Oral Contraception and Thromboembolic Disease. J. Coll. Gen. Pract., *13*:267-279. 1967.

[2] Inman, W.H.W. and Vessey, M. P. Investigation of Deaths from Pulmonary Coronary and Cerebral Thrombosis and Embolism in Women in Child Bearing Age, Brit Med J. *2*:193-199. 1968.

[3] Vessey, M. P. and Doll. R. Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit Med J, *2*:651-657, 1969.

[4] Sartwell, P. E., Masi. A. T., Arthes, F. G., Greene, G. R., and Smith, H. E., Thromboembolism and Oral Contraceptives: An Epidemiological Case-Control Study. Am. J. Epidem. 90:365-380, (November) 1969.

The estimate of the relative risk of thromboembolism in the study by Vessey and Doll[3] was about seven fold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as non-users. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long continued administration. The American study was not designed to evaluate a difference between products. However, the study suggested that there might be an increased risk of thromboembolic disease in users of sequential products. This risk cannot be quantitated, and further studies to confirm this finding are desirable. Retrospective studies in Great Britain have shown a statistically significant association between cerebral thrombosis and embolism and the use of oral contraceptives. This has not been confirmed in the United States.

2. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

3. Since the safety of * * * in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the time of the first missed period.

4. A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long range effect to the nursing infant cannot be determined at this time.

PRECAUTIONS

1. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs, including Papanicolaou smear since estrogens have been known to produce tumors, some of them malignant, in five species of subprimate animals.

2. Endocrine and possibly liver function tests may be affected by treatment with * * *. Therefore, if such tests are abnormal in a patient taking * * *, it is recommended that they be repeated after the drug has been withdrawn for 2 months.

3. Under the influence of estrogen-progestogen preparations, pre-existing uterine fibromyomata may increase in size.

4. Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

5. In breakthrough bleeding, and in all cases of irregular bleeding per vaginam, nonfunctional causes should be borne in mind. In undiagnosed bleeding per vaginam, adequate diagnostic measures are indicated.

6. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

7. Any possible influence of prolonged * * * therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

8. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving * * * therapy.

9. The age of the patient constitutes no absolute limiting factor, although treatment with * * * may mask the onset of the climacteric.

10. The pathologist should be advised of * * * therapy when relevant specimens are submitted.

11. Susceptible women may experience an increase in blood pressure following administration of contraceptive steroids.

ADVERSE REACTIONS OBSERVED IN PATIENTS RECEIVING ORAL CONTRACEPTIVES

A statistically significant association has been demonstrated between use of oral contraceptives and the following serious adverse reactions:

Thrombophlebitis

Cerebral thrombosis

Pulmonary embolism

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

The following adverse reactions are known to occur in patients receiving oral contraceptives:

Nausea

Vomiting

Gastrointestinal symptoms (such as abdominal cramps and bloating)

Breakthrough bleeding

Spotting

Change in menstrual flow

Amenorrhea during and after treatment

Edema

Chloasma or melasma

Breast changes: tenderness, enlargement and secretion

Change in weight (increase or decrease)

Changes in cervical erosion and cervical secretions

Suppression of lactation when given immediately post-partum

Cholestatic Jaundice

Migraine

Rash (Allergic)

Rise in blood pressure in susceptible individuals

Mental depression

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted:

Anovulation post treatment	Fatigue
Premenstrual-like syndrome	Backache
Changes in libido	Hirsutism
Changes in appetite	Loss of scalp hair
Cystitis-like syndrome	Erythema multiforme
Headache	Erythema nodosum
Nervousness	Hemorrhagic eruption
Dizziness	Itching

The following laboratory results may be altered by the use of oral contraceptives:

Hepatic function: Increased sulfobromophthalein retention and other tests	Thyroid function: Increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values
Coagulation tests: Increase in prothrombin, Factors VII, VIII, IX, and X	Metayrapone test
	Pregnanediol determination

Dosage And Administration

This section includes routine administration and specific instructions on handling problems such as breakthrough bleeding, amenorrhea, etc.

Clinical Studies (An Optional Section)

If any clinical data are included, the following paragraph must be used: Different pregnancy and adverse reaction rates have been reported with the use of each oral contraceptive. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, pregnancy and adverse reaction rates tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen and did not discontinue due to adverse reactions or pregnancy. In clinical trials with * * * patients completed * * * cycles, and a total of * * * pregnancies was reported. This represents a pregnancy rate of * * * per 100 woman years. Please see the SPECIAL NOTE in this labeling.

Office - Supreme Court, U.S.
FILED
OCT 10 1984
ALEXANDER L. STEVAS
CLERK

No. 84-290

In the Supreme Court of the United States

October Term, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

vs.

CAROL LYNN WOODERSON,
Respondent.

BRIEF IN OPPOSITION TO A PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF KANSAS

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BEST AVAILABLE COPY

QUESTIONS PRESENTED FOR REVIEW

Respondent asserts that a Writ of Certiorari should not be issued. The Kansas Supreme Court entered a judgment in this proceeding which should be recognized by this Court and affirmed. Such recognition will dispose of the following issues:

1. The right of a state court to determine and assess compensatory and punitive damages against a defendant who is regulated by the Federal Government and markets its product in that state.

2. The right of a state court to determine the adequacy of prescription drug warnings given the regulation of said subject matter by the Food and Drug Administration.

3. The right of a state court to rule upon the applicability of its own comparative negligence statutes to a case in controversy and/or the submission of an issue of comparative negligence to a jury.

4. The justiciability of issues that have been rendered moot by a decision of the United States Supreme Court.

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No. 84-290

In the Supreme Court of the United States

October Term, 1984

ORTHO PHARMACEUTICAL CORPORATION,
Petitioner,

vs.

CAROL LYNN WOODERSON,
Respondent.

BRIEF IN OPPOSITION TO A PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME COURT OF THE STATE OF KANSAS

OPINIONS BELOW

The opinion of the Supreme Court of Kansas dated April 27, 1984, reported at 235 Kan. 387, 681 P.2d 1038, are reproduced in Appendix A of petitioner. This was a direct appeal from the judgment entered by the trial court on a verdict returned in February, 1983. On March 18, 1983, the trial court orally denied Ortho Pharmaceutical Corporation's Motions for a Directed Verdict or in the Alternative for a New Trial (R. XL).[1]

JURISDICTION

The Court's decision in *Silkwood v. Kerr-McGee*, ... U.S. ....., 104 S. Ct. 615 (1984), renders moot the issues raised by petitioner and absent the requisite justiciability, this Court is without subject matter jurisdiction to hear the same.

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1. Citations to "R. ....." are to the trial record; "pp. ....." refers to the trial transcript.

STATEMENT OF THE CASE

This is the case of a statistic which has been described as unconvincing and uncorroborated.

Carol Lynn Wooderson brought her action in the District Court of Sedgwick County, Kansas, for damages for personal injuries which she claims resulted from her ingestion, over a period of years, of the oral contraceptive Ortho-Novum 1/80, manufactured by the petitioner, Ortho Pharmaceutical Corporation (Ortho). Mrs. Wooderson alleged that Ortho knew, or should have known, of the dangerous side effects of its products based upon its position as an expert in the field, upon its research, upon cases reported to it, and upon scientific development, research, and publications in the field.

Ortho alleged that scientific studies of its drugs by disinterested research groups had not proven an association between the use of Ortho-Novum 1/80 and Hemolytic Uremic Syndrome (HUS), malignant hypertension, and acute renal failure, and that it therefore, had no duty to warn of the same. Ortho also claimed that, assuming arguendo that they did have knowledge of said side effects, the Food and Drug Administration (FDA) had rejected a proposal from the G. D. Searle & Co. pertaining to the inclusion of HUS as an adverse reaction associated with the use of Ortho-Novum 1/80 because the reports of HUS were anecdotal, and not based on well controlled scientific studies (none of which were conducted by Ortho) in accordance with the statute and regulations.

The Kansas Supreme Court found:

> The expert testimony and the exhibits in this case disclose that there was an abundance of published information in the medical journals, prior to and

during the years when plaintiff was taking Ortho-Novum 1/80, which linked the use of oral contraceptives with HUS, malignant hypertension, and acute renal failure. . . . The available scientific literature clearly tended to show that there was a danger of HUS, malignant hypertension and acute kidney failure attendant to the use of the drug.

Wooderson v. Ortho Pharmaceutical Corp., 235 Kan. 387 at 408-409, 681 P.2d 1038 at 1056-1057 (1984).

The Kansas Supreme Court also found:

On April 10, 1970, Ortho sent a Sales Bulletin on the subject of Ortho-Novum labeling changes to its "detail men," sales representatives of the manufacturer who call directly upon the physicians. That bulletin quoted extensively from the first paragraph of the acting commissioner's (FDA) letter, but made no mention of the third paragraph concerning the British Committee's advice to physicians in England. On May 15, 1970, Ortho sent out another Sales Bulletin, this one on the subject of *The Report of the British Committee on the Safety of Drugs*. This bulletin did not quote the third paragraph of the acting commissioner's letter, but was obviously written in response thereto. It indicated that Ortho's own analysis of the British data indicates that there is no statistically significant difference between 50, 75/80 and 100 micrograms of mestranol. It stated that products containing 75/80 gammas of mestranol show a risk as low if not lower than 50 gamma products. It urged the continued sale of its 80 gamma product, and cautioned its sales people not to be "stampeded" with the number 50. A July 6, 1970, Sales Bulletin continued to urge sale of Ortho-Novum 1/80, and

urged concentration on Ortho-Novum 1/50 only if the physician "is very concerned with using lowest estrogen activity." For physicians who asked about switching patients to lower estrogen level products, the bulletin suggested that detail men respond:

"Doctor, nothing in this British data offers enough sound evidence to cause you to switch patients who are on 100 gamma of mestranol. We have been saying for years and continue to say that it makes sense to use the least activity of any drug that will effectively accomplish its purpose; therefore, you may wish to move patients to low activity products such as ORTHO-NOVUM 1/80 or ORTHO-NOVUM 1/50."

In short, this evidence indicated that Ortho played down the British report and continued to urge sale of its higher estrogen product until Ortho itself could be entirely satisfied that the product was causing damage. Apparently its competitive posture in the market was better served by continuing the manufacture and sale of its 1/80 product, since other manufacturers were also producing the 1/50 dosage.

Another area which plaintiff emphasizes is that of the "Irey-type" lesions. Dr. Nelson S. Irey, of the Armed Forces Institute of Pathology, issued a report in 1969, and published it in a pathology journal in 1970. The blood vessels of some forty women had been examined posthumously. Lesions were found in the inner wall or intima of the blood vessels of every one of the bodies of those women who were known to have been taking oral contraceptives; no such changes were found in the bodies of those who had *not* been taking oral contraceptives. In spite of this report linking oral contraceptives to vessel wall

> damage, Ortho did no further animal research to prove or disprove the proposition put forth by Irey: that oral contraceptives cause vessel wall damage.

Wooderson, supra, at 419.

At the conclusion of a six-week trial, the jury returned a verdict and the Court entered judgment for respondent and against Ortho for actual damages of $2,000,000 and punitive damages of $2,750,000. The Supreme Court of Kansas affirmed the verdict on appeal.

SUMMARY

The respondent submits that once a drug manufacturer has performed a sufficient amount of testing to acquire approval from the Food and Drug Administration, it is duty bound to continue testing and evaluating its products. The manufacturer cannot wait until there is absolute statistical proof to support the need for additional testing and/or the promulgation of warnings necessary to apprise the prescribing physician of the risks associated with the ingestion of their product.

The Kansas Supreme Court's ruling in *Wooderson v. Ortho Pharmaceutical Corp.,* 235 Kan. 387, 681 P.2d 1038 (1984), encourages manufacturers of prescription drugs to adequately test their products so that they will be able to warn of risks attendant with consumption of their product. The petitioner cannot deny that statistically proven results regarding known hazards will be approved by the FDA for labeling, even at the expense of adding "clutter" to an extended list of warnings that must accompany the distribution of prescription drugs within a given state.

Respondent further submits that the goals of the Food and Drug Administration are to regulate the manufacture and marketing of prescription drugs. By its decision, the Kansas Supreme Court is not attempting to promulgate laws governing the manufacture or marketing of prescription drugs. They are not impinging upon the bailiwick of the Food and Drug Administration in any way. This is a civil action in which the Kansas Courts, through the application of common law principles of negligence and strict liability in tort, are protecting the rights of its citizens.

REASONS FOR DENYING PETITION

I. Silkwood v. Kerr-McGee Corp., ... U.S. ....., 104 S. Ct. 615 (1984).

The State's traditional authority to provide tort remedies to its citizens and the Federal Government's regulatory authority in certain spheres of interest are to be considered in the case at bar.

Amicus would characterize this Court's holding in *Silkwood*, as an expression of the proposition that State tort remedies enjoy no special immunity from Federal preemption.

The petitioners tell us that the State's ability to grant an award of punitive damages, in an industry that is regulated by the Federal Government, was left open by this Court's decision in *Silkwood*.

Respondent respectfully submits that the foregoing arguments of counsel constitute a "mislabeling" of this Court's holding in *Silkwood* and the rationale therefor.

In *Silkwood*, this Court held that:

> Insofar as damages for radiation injuries are concerned, preemption should not be judged on the basis that the federal government has so completely occupied the field of safety that state remedies are foreclosed but on whether there is an irreconcilable conflict between the federal and state standards or whether the imposition of a state standard in a damages action would frustrate the objectives of the federal law.

....., 104 S. Ct. at 622, 626.

As this Court recently observed in *Pacific Gas & Electric Co. v. State Energy Resources Conservation & Development Comm'n*, ... U.S. ....., 103 S. Ct. 1713, 75 L. Ed.2d 752 (1983), State law can be preempted in either of two general ways. If Congress evidences an intent to occupy a given field, any State law falling within that field is preempted. *Id.* at ....., 103 S. Ct. 1722; *Fidelity Federal Savings & Loan Ass'n v. Dela Cuesta*, 458 U.S. 141, 153, 102 S. Ct. 3014, 3022, 73 L. Ed.2d 664 (1982); *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230, 67 S. Ct. 1146, 1152, 91 L. Ed. 1447 (1947). If Congress has not entirely displaced State regulation over the matter in question, state law is still preempted to the extent it actually conflicts with Federal law, that is, when it is impossible to comply with both State and Federal law, *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-143, 83 S. Ct. 1210, 1217-1218, 10 L. Ed.2d 248 (1963), or where the state law stands as an obstacle to the accomplishment of the full purposes and objectives of Congress, *Hines v. Davidowitz*, 312 U.S. 52, 67, 61 S. Ct. 399, 404, 85 L. Ed. 581 (1941). *Pacific Gas & Electric Co., supra*, at ....., 103 S. Ct. at 1722.

The Court initially must approach the question of Federal preemption from the viewpoint that a finding of preemption is the exception rather than the rule. *Cosmetic, Toiletry & Fragrance Ass'n, Inc. v. State of Minnesota,* 440 F. Supp. 1216 (D. Minn. 1977), U.S.C.A. Const., Art. 6, Cl. 2.

If Congress is authorized to act in a field, it should manifest its intention clearly It will not be presumed that a Federal statute was intended to supersede the exercise of the power of the State unless there is a clear manifestation of intention to do so. The exercise of Federal supremacy is not lightly to be presumed. *Schwartz v. Texas,* 344 U.S. 199, 202-203, 73 S. Ct. 232, 235, 97 L. Ed. 231 (1952).

Given this point of departure, the Court must examine the language and purpose of the Federal statute, its legislative history, its field of operation, and points of literal and practical conflict between the Federal and State enactments to determine whether the heavy burden of demonstrating preemption has been met.

A comprehensive opinion dealing with the format for judicial analysis when a preemption issue is raised is that of former Chief Judge Matthes in *Northern States Power Co. v. State of Minn.,* 447 F.2d 1143, 1146-47 (8th Cir. 1971), *Aff'd,* 405 U.S. 1035, 92 S. Ct. 1307, 31 L. Ed.2d 576 (1972). The prescribed analysis is basically four tiered. In this case, the second and fourth steps are disputed. That is, with regard to steps one and three, no one contends that the FDA exceeded its statutory authority in promulgating the Federal rules in question, that Congress acted unconstitutionally in permitting this type of regulation under the Food, Drug and Cosmetic Act, or of critical importance herein, that the Food, Drug

and Cosmetic Act contains express preemption provisions. Of issue herein is the doctrine of implied preemption and, as alleged by the petitioner and Amicus, the physical impossibility of compliance with the Federal regulations and tort law concepts respecting the same.

In regard to the issue of implied preemption, Judge Matthes, in *Northern States Power Co.*, articulated four key factors in determining whether preemption of a particular area of regulation has occurred. These factors, distilled from the many cases which have considered preemption questions, are:

> (1) The aim and intent of Congress as revealed by the statute itself and its legislative history . . .; (2) The pervasiveness of the federal regulatory scheme as authorized and directed by the legislation and as carried into effect by the federal administrative agency . . .; (3) The nature of the subject matter regulated and whether it is one which demands "exclusive federal regulation in order to achieve uniformity vital to national interests." . . .; and (4) "Whether under the circumstances of [A] particular case [state] law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Northern States Power Co., supra,* at 1146-47).

Turning to the first of these four factors, the petitioner and Amicus have cited numerous regulations, abstract portions of legislative history, and have tacked the same together to resemble an argument.

The petitioner would have this Court believe that not only does the FDA proscribe minimum requirements for labeling purposes, but that they proscribe "optimal" requirements. In support of this proposition, the peti-

tioner argues that the FDA's rejection of some 15 proposed labeling changes, including "some" language pertaining to Hemolytic Uremic Syndrome (the record is devoid of any evidence respecting the actual language employed), when read together with 21 C.F.R. 1.21(c)(1), is clearly indicative of the FDA's position with respect to the non-inclusion of HUS as a possible side effect or adverse effect of that drug which is the subject matter of the case at bar.

The Kansas Supreme Court addressed this proposition and rejected the same noting:

> The letter cannot be construed as a clear determination by the FDA that contraceptive induced HUS does not merit warnings and thus this argument has no merit.

Wooderson v. Ortho Pharmaceutical Corp., supra, at 409.

The Amicus have also abstracted selected portions of legislative history dealing with the definitional sections of 21 C.F.R. 201.57 and have read the same together with 21 C.F.R. 201.200 dealing with the efficacy claims of drug manufacturers. The Amicus would then submit to this Court that the limiting language of the efficacy section and the corresponding proof required under 21 C.F.R. 201.200 to obtain an "effective" classification from the National Academy of Sciences-National Research Council-Drug Efficacy Study Group, somehow supports the proposition that warnings without absolute documentation or representative studies respecting the same will be prohibited by the FDA. The pathetic conclusion of such a proposition is inescapable, i.e., until the control group (the consumer) has a representative number of casualties, and a disinterested research foundation, such as the British Committee on Safety of Drugs, initiates an

investigation pertaining to the incidence of injury and subsequently develops proof pertaining to the same, that the manufacturer is in the meantime "prohibited" from warning the consumer of "undocumented" suspected adverse reactions for which "an association has neither been confirmed nor refuted" and is thereby isolated from liability respecting the same.

Fortunately, for the sake of the consumer, this Court, by virtue of its decision in *Silkwood,* still permits the states and a jury of one's peers, to decide each case upon the evidence submitted in order to determine whether or not the manufacturer in question is responsible for its failure to test and warn individuals, such as the plaintiff herein, who has become an unconvincing and uncorroborated statistic.

In regard to the second factor of the preemption considerations, this respondent readily concedes that Congress, through the Food and Drug Administration, has expressed an intent to occupy the field in terms of the manufacture and distribution of prescription drugs. Congress has, through the FDA, gone one step further in terms of labeling requirements and admonitions pertaining to efficacy claims of the manufacturer. 21 C.F.R. § 201.57, et seq.

As was true in *Silkwood,* any evidence of the intent of Congress to preclude the States from providing traditional State law remedies for its citizens, is conspicuously absent from the Briefs of the petitioner and Amicus and more importantly, from the dispositive regulations concerned. As this Court noted in *Silkwood*:

> This silence takes on added significance in light of Congress' failure to provide any federal remedy for persons injured by such conduct. It is difficult to believe that Congress would, without comment, re-

move all means of judicial recourse for those injured by illegal conduct. *United Construction Workers v. Laburnum Corp.*, 347 U.S. 656, 663-664, 74 S. Ct. 833, 836-838, 98 L. Ed. 1025 (1954).

Unlike *Silkwood*, and in support of the respondent's position, there is no legislation akin to that of the Price-Anderson Act which evidenced an intent by Congress to make compensation available to victims of a nuclear accident.

In regard to the third and fourth factors in preemption questions, this Court must decide whether or not the subject matter regulated is one which demands "exclusive federal regulation in order to achieve uniformity vital to national interests" and whether or not, under the circumstances of a particular case [State] law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress. At the risk of belaboring this point, the respondent would concur with this Court's conclusion in *Silkwood*, which is applicable herein, wherein it was noted that by not providing for the same (damages) Congress assumed that traditional principles of State Court law would apply with full force unless they were expressly supplanted. Thus, it is Ortho's burden to show that Congress intended to preclude such awards. *I.B.E.W. v. Foust*, 442 U.S. 42, 53, 99 S. Ct. 2121, 2128, 60 L. Ed.2d 698 (1979) (Blackmun, J., concurring).

By failing to address the issue of remedies, Congress had to assume that State law remedies, in whatever form they might take, were available to injured claimants. This was so, even though Congress was well aware of the FDA's exclusive authority to regulate the manufacture and marketing of prescription drugs.

As this Court notes, in both its majority and dissenting opinions, there will no doubt be tension between the conclusion that safety regulation, and in this case manufacture and marketing regulation, is the exclusive concern of the Federal law and the conclusion that a State may nevertheless award damages based on its own law of liability.

It may be that the award of damages based upon a State's law of negligence or strict liability is regulatory in the sense that, in this case a pharmaceutical manufacturer, will be threatened with damages liability if it does not conform with State standards, but that regulatory consequence was something that Congress was quite willing to accept.

As far as damages caused by pharmaceuticals are concerned, the test should be a reflection of this Court's holding in *Silkwood,* i.e.:

> The preemption should not be judged on the basis that the federal government has so completely occupied the field of safety that state remedies are foreclosed but on whether there is a irreconcilable conflict between the federal and state standards or whether the imposition of a state standard in a damages action would frustrate the objectives of the federal law.

The facts in the case at bar, perhaps even more so than the facts in *Silkwood,* militate in favor of finding no such conflict or frustration.

II. Decisional Law Supports the Right of the States to Determine the Adequacy of Prescription Drug Warnings.

Carol Wooderson produced evidence sufficient for the jury to conclude there is an association between the use of oral contraceptives and Hemolytic Uremic Syndrome,

malignant hypertension and acute kidney failure. Given this association, Ortho was obliged to include warnings of that association. Since there is evidence to support the jury's conclusion that an association exists, Ortho is not entitled to now remarshal those facts favorable to its argument in hopes that this Court will sit as a second trier of facts.

Defendant, according to its argument in the lower Courts, would have the Court believe Comments j and k of Section 402A, Restatement (Second) of Torts, somehow provide them with a blank check to market dangerous drugs however they see fit, yet never have to pay the piper. According to the defendant, Comment j requires "proof the drug maker has knowledge or by application of reasonably developed human skill and foresight should have knowledge of the presence of an increased risk." (Appellant's Brief at 11). In fact, Comment j speaks of "knowledge of the presence of *the ingredient* and the danger. Likewise, in the case of poisonous drugs, or those unduly dangerous for other reasons, warning as to use may be required." This case is about an unduly dangerous drug, not about eggs or strawberries, nor about alcoholic beverages or saturated fats.

According to the petitioner and Amicus, the seller is not responsible "unless he fails to give proper warning of the risks" which responsibility is held in check by the regulatory scheme of the Food and Drug Administration. In the lower Courts, the petitioner's assertion was capsulized in the defendant's Proposed Instruction No. 16 which, as indicated above, states that the seller is not responsible "unless he fails to give proper warning of the risks." This, however, was the substance of the instructions given.

The manufacturer of a dangerous drug is duty bound to provide an adequate warning. *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981); *Ortho Pharmaceutical Corp. v. Chapman*, 388 N.E.2d 541 (Ind. App. 1979). Unless the FDA requires otherwise, as it does with oral contraceptives (R. LXXV, pp. 38-39), the warnings need only be made to the doctor. *Lindsey v. Ortho Pharmaceutical Corp.*, 637 F.2d 87 (2d Cir. 1980). Still when information is provided by the manufacturer, it must not mislead and misinform the recipient. *Seley v. G. D. Searle & Co.*, 67 Ohio St.2d 192, 423 N.E.2d 831 (1981). Carol Wooderson testified she was misled by Ortho's patient information booklet. (Exhibit 6, R. XXXXVI, p. 8; R. VI, pp. 114, 120-124, 137-144). Ortho's effort to duck its responsibility to warn of the risk of Hemolytic Uremic Syndrome, malignant hypertension and kidney failure is based upon the theory that if one does not know to a scientific certainty, one need not do anything. This is not the law.

> A jury may find that a warning is inadequate and unreasonable even where the existence of a "risk," i.e., a causal relationship between the use of the product and resulting injury, has not been definitely established. *McCue v. Norwich Pharmacal Co.*, (C.A. 1, 1972) 453 F.2d 1033; *Hamilton v. Hardy* [37 Colo. App. 375, 549 P.2d 1099 (1976)]. Thus, where scientific or medical evidence exists tending to show that a certain danger is associated with use of the drug, the manufacturer may not ignore or discount that information in drafting its warnings solely because it finds it to be unconvincing. *Mahr v. G. D. Searle & Co.* [72 Ill. App.3d 540, 564, 28 Ill. Dec. 624, 390 N.E.2d 1214 (1979)].

Seley v. G. D. Searle & Co., 423 N.E.2d at 837.

In *Skill v. Martinez,* 91 F.R.D. 498 (D. N.J. 1981), *Aff'd,* 677 F.2d 368 (3d Cir. 1982), Ortho is singing another verse of the same tune. Plaintiff suffered a cerebral vascular accident, or a stroke, resulting from her ingestion of an unspecified dosage of Ortho Novum in conjunction with smoking. When Ortho's argument that Mrs. Skill had to prove the cause of her stroke to an absolute certainty was rejected, there was still Ortho's first fall back position. There was, Ortho insisted, no duty to warn. Ortho argued the warnings about the risks of stroke were admittedly adequate, and these warnings should be enough. There was, however, no warning about smoking while on the pill.

> Ortho argues that the medical literature did not support the jury's finding that the drug company should have warned of this risk. It opines that it is not sufficient for respected scientists to indicate that the risk of stroke was greater when pills are taken combined with smoking, because those scientists also say they would like larger samples. The basic question the jury had to answer boiled down to this: Was there sufficient knowledge, at the relevant time, of danger inherent in taking the pill while smoking to compel Ortho's giving of proper warnings in this regard? The jury answered "Yes" and the Court cannot quarrel with that answer.

91 F.R.D. at 514.

In *Ortho Pharmaceutical Corp. v. Chapman,* 388 N.E. 2d 541 (Ind. App. 1979), Ortho offered expert opinion that the causal relationship between oral contraceptives and thrombophlebitis had not been established. It argued "There should be no liability for the failure to state what is not proved true." 388 N.E.2d at 544. The Court held

that the question of the relationship was one for the jury. "Clearly we cannot find as a matter of law that the warnings were adequate." *Id.*

Dr. Pasquale, Ortho's clinical director, testified "If those case reports are reasonable evidence of an association, *we should have changed the package insert, yes*" (R. XXXII, p. 2377). How many pages there are in some medical texts (Appellant's Brief at 15, n. 17), cannot change the content nor the import of the testimony of the clinical director of Ortho Pharmaceutical that if a jury finds it more likely than not that the case reports established "reasonable evidence of an association" then Ortho should have changed the package insert.

Defendant contends that compliance with the Food and Drug Administration requirements somehow lets Ortho off the hook. The jury was properly instructed on this issue in Instruction No. 9:

> Evidence that a manufacturer has complied with applicable regulations or industry standards in the labeling of its product constitutes evidence of due care on the part of the manufacturer but it is not conclusive. Such evidence may be considered by you in determining whether or not the warnings given were adequate. Such a compliance does not relieve a manufacturer of the duties set forth in these instructions.

(R. II, p. 304).

In *Ortho v. Chapman, supra,* the Court noted it could not find the warnings adequate as a matter of law, "nor does Ortho's compliance with federal law require a different result." 388 N.E.2d at 554.

In *Bristol Myers Co. v. Gonzales,* 548 S.W.2d 416 (Tex. App. 1976), *Rev'd on other grounds,* 561 S.W.2d

801 (Tex. 1978), the Court rejected the argument that compliance with FDA requirements makes a warning adequate as a matter of law. On review, this holding was specifically endorsed by the Supreme Court of Texas. 561 S.W.2d at 804.

In *Jones v. Hittle Service, Inc.*, 219 Kan. 627, 549 P.2d 1383 (1976), the Court held compliance with administrative standards was evidence of due care, but that such compliance does not preclude a finding of negligence or a product defect if a reasonable person would do more.

In summarizing Ortho's argument it had no duty to warn, they purport to make four points. Respondent has never demanded "prolix compendium" of anything. Carol Wooderson has simply proved there should have been a warning about Hemolytic Uremic Syndrome, malignant hypertension and acute kidney failure. She has also proved Ortho failed to apprise doctors of the relative risks of various dosages of synthetic estrogen in Ortho-Novum products. She has proved that the risk was real, although Ortho apparently likes to think the loss of both kidneys is minor. There is nothing in the record about what doctors read and what they ignore, and Ortho certainly has not proved that doctors are provided with adequate warnings, they cannot understand or do not believe.

Respondent has proved to the jury's satisfaction that there was substantial evidence of the association between oral contraceptives and Hemolytic Uremic Syndrome, malignant hypertension and acute kidney failure. Even Ortho's clinical director agreed that, on that assumption, "we should have changed the package insert," and that "[w]e would be misbranding" (R. XXXII, p. 2377). Ortho did have a duty to warn, and the jury's finding should

not be disturbed. To ask this Court to review the prior trial and the Kansas Supreme Court's decision is preposterous. This would indeed be a busy Court if it had to review all such State Court decisions.

III. The Award of Punitive Damages Is Consistent With the Holding in Silkwood v. Kerr-McGee Corp. and Is Supported by the Evidence.

Once again, the respondent submits that this Court's holding in *Silkwood* is applicable and dispositive of the Kansas Court's ability to assess punitive damages against a defendant under the circumstances of the case at bar.

As was true in *Silkwood,* the award of punitive damages in this case does not conflict with the Federal remedial scheme under which the FDA is authorized to impose civil penalties on drug manufacturers for violation of Federal standards. Paying both Federal fines and State imposed punitive damages for the same incident is not physically impossible, nor does exposure to punitive damages frustrate any purpose of the Federal remedial scheme. By failing to provide an adequate remedy for those who are injured by prescription drugs, Congress in effect has said that it is not inconsistent to vest the FDA with regulatory authority over the manufacture and marketing of prescription drugs while at the same time allowing plaintiffs like Wooderson to recover for injuries caused by said drugs.

The respondent further submits that this Court need not reach the basis for the jury's award of punitive damages given the applicability of *Silkwood* as aforesaid. In deference to Carol Lynn Wooderson, the respondent does add that the record below is replete with proof respecting the actionable conduct of the petitioner including, but not

limited to, failing to warn of and test for Irey-type lesions after having obtained causational knowledge respecting the same and instructing its salesman to negate the FDA's Dear Doctor letters. Enough said.

IV. Under the Circumstances of the Case at Bar, the Petitioner's Allegations Regarding Comparative Fault Are Unfounded and Without Merit.

Throughout the course of the petitioner's appeals, they have tried repeatedly to remedy their trial strategy in regard to the issue of comparative fault. The Kansas Supreme Court dealt with this particular allegation and disposed of the same by finding that:

> Ortho's position was clearly stated: *It made no claim that the physicians departed from approved medical practice,* and it intended to offer no evidence that the physicians did anything wrong. If the plaintiff's evidence were to disclose fault on the part of the physicians, Ortho reserved the right to argue that. When the matter went to trial, plaintiff offered no evidence of causal negligence on the part of the physicians, and thus it was not necessary for the trial court to submit that issue to the jury. There was no evidence, expert or otherwise, of actionable, causal negligence on the part of Drs. Hermes and Wilcox. Under the circumstances disclosed by the record and the evidence in this case, we conclude that the trial court did not err in refusing to submit the issue of the comparative negligence of the physicians to the jury.
>
> As to the claimed negligence on the part of plaintiff, Ortho points only to the evidence that plaintiff did not go to the hospital emergency room on June 25

after she was told by her physician to do so if she did not get better by 6:00 o'clock that evening. Whether she felt better by evening, we do not know. There is no testimony, medical or otherwise, which suggests that this failure to go to the hospital on June 25, caused or contributed to her injuries or that her condition was reversible on June 25. She saw Dr. Wilcox on June 28, and he did not send her to the hospital at that time. There is, however, testimony that diagnosis and treatment several months earlier might have averted the disaster. We find no evidence to support the submission of Mrs. Wooderson's causal negligence to the jury. (Emphasis supplied by the Kansas Supreme Court) *Wooderson, supra,* at 414.

V. Given the Overall Applicability of the Holding in Silkwood, the Requisite Case or Controvery Is Non Existent and the Issues Presented Are Therefore Non Justiciable.

Baker v. Carr, 396 U.S. 186, 86 S. Ct. 691, 7 L. Ed.2d 663 (1962), and its progeny have established a long line of precedent which has been repeatedly recognized by this Court in a plethora of decisional law. The respondent submits that the facts in the case at bar are perhaps a better example of the fact situation in *Silkwood* for the applicability of holdings therein to the proposition submitted by the respondent.

The respondent respectfully submits that this Court should recognize its holdings in *Silkwood* and the applicability thereof to the case at bar and find therefore that the issues presented are non justiciable.

CONCLUSION

Nine Justices of the Supreme Court act in concert with one another to determine the course of decisional law and in a practical sense, the history of the United States of America. By its holding in *Silkwood*, this Court permits the States to protect their citizens and compensate them when they have been wronged by another.

The petitioner and Amicus repeatedly entreat this Court to undermine the jury's verdict and decide the case the way they argued the facts. They ask the Court to reverse this verdict because, to Ortho, it seems "irrational and unsound."

Many are the cases in which one side or the other feels that the result is irrational and unsound. If this were the test of a verdict, finality would be rare indeed. Carol Wooderson has gotten a verdict to which the evidence shows she is entitled. It should be affirmed. This Court has not and should not establish a policy of reviewing State Court trials and decisions such as this one. The Petition should be denied.

Respectfully submitted,

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